



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07F 9/6561, A61K 31/675		A1	(11) International Publication Number: WO 00/18775 (43) International Publication Date: 6 April 2000 (06.04.00)
<p>(21) International Application Number: PCT/GB99/03207</p> <p>(22) International Filing Date: 27 September 1999 (27.09.99)</p> <p>(30) Priority Data: 9821058.6 28 September 1998 (28.09.98) GB</p> <p>(71) Applicants (<i>for all designated States except US</i>): UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED [GB/GB]; P.O. Box 497, Cardiff CF1 3XR (GB). REGA FOUNDATION [BE/BE]; Minderbroedersstraat 10, B-3000 Leuven (BE).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): MCGUIGAN, Christopher [GB/GB]; 2 Alfreda Road, Whitchurch, Cardiff CF4 2EH (GB). BALZARINI, Jan [BE/BE]; Kapeldreef 20, B-3001 Heverlee (BE).</p> <p>(74) Agent: HOWARD, Paul, Nicholas; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: ANTIVIRAL PURINE DERIVATIVES</p> <p>(57) Abstract</p> <p>Chemical compounds comprising nucleoside phosphoramidates, their preparation and their therapeutic use in treating viral infections, particularly HIV and HBV are disclosed. The compounds contain a substituted adenine analogue moiety comprising 2-amino-6-(cyclopropylamino)-9H-purin-9-yl. The compounds show both anti-viral activity and acid stability. Salts and esters of the phosphoramidates are included. A representative compound is (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-alaniny)]-phosphate.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ANTIVIRAL PURINE DERIVATIVES

- The present invention relates to a chemical compound. In particular the present invention
5 relates to a chemical compound suitable for use as an anti-viral agent. The present invention also relates to the therapeutic use of the present chemical compound, to a pharmaceutical composition containing the present compound and to use of the present compound in the manufacture of a medicament.
- 10 Since the recognition of human acquired immunodeficiency syndrome (AIDS) much interest and research activity has been directed to its understanding and to attempting to provide a means of treatment. The human immunodeficiency virus (HIV) has been identified as the presumed aetiological agent in AIDS. A large literature now exists related to the use of a wide variety of chemical compounds having as their object a demonstration
15 of anti-viral activity with respect to HIV, hepatitis B virus (HBV), herpes and other viruses.

A class of compounds which has demonstrated anti-viral activity and which has been the subject of a large amount of research are nucleoside analogues.

20 An example of such a compound is "Abacavir" which is a substituted adenine analogue (Foster R.H. & Faulds D. Drugs 1998 55 729-736). This compound has entered clinical use due to the potential activity and stability of the compound displayed in preliminary work.

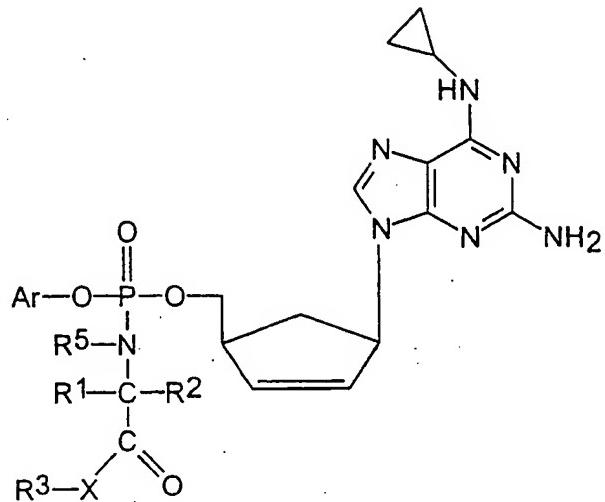
25 PCT/GB96/00580 relates to a class of nucleoside analogues said to be highly active with respect to HIV. In particular PCT/GB96/00580 addresses the problem of providing compounds which are said to be highly potent *in vitro* viral inhibitors in both TK⁻ and TK⁺ cells. The compounds disclosed in PCT/GB96/00580 are phosphoramidates of purine or
30 pyrimidine nucleoside analogues. Such compounds can however display chemical, for example acid, or biological, for example nucleoside phosphorylase, instability towards glycoside bond cleavage. Consequential deactivation may limit their potential clinical efficacy.

A compound however to be potentially useful in a clinical setting needs to exhibit a number of other properties as well as demonstrating, at least in *in vitro* tests, a sufficient and desired anti-viral activity. Primarily, these other properties comprise good pharmacokinetic properties, sufficient stability in the compound to permit its ease of handling and supply, and sufficiently low toxicity to permit its administration with an acceptable level of side effects to a patient in need of treatment for the viral infection in question.

10 In practice however it is frequently found that attempts to modify a compound demonstrating anti-viral activity *in vitro*, in order to improve its other properties, can have a detrimental effect on the anti-viral activity it displays. Ideally moreover any compound proposed for clinical trials needs also to have a ready means of administration and to be preparable by an economically viable route.

15 It is an object of the present invention to provide a novel class of compounds exhibiting potent anti-viral, in particular anti HIV and/or HBV activity, in combination with good pharmacokinetic and stability properties and exhibiting sufficiently low toxicity so as to provide a compound having beneficial properties for clinical use.

According to the present invention there is provided a compound according to the following formula (I):



5 wherein

Ar is an aryl group,

R¹ and R² are independently selected from the group comprising H, alkyl and aryl groups;

10

X is selected from the group comprising O, NH, NR⁴ and S wherein R⁴ is selected from the group comprising alkyl and aryl groups;

15

R⁵ is selected from the group comprising H, alkyl and aryl groups, wherein when R¹ and R⁵ are each alkyl they may be linked to form a 5- or 6- membered ring;

and R³ is selected from the group comprising H, alkyl, aryl, heterocyclic and polycyclic groups,

20 or a pharmaceutically acceptable derivative or metabolite thereof.

The present invention includes salts and physiologically functional derivatives of the presently defined compounds.

Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more 5 preferably C₅ to C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₆, more preferably C₁ to C₆, more preferably methyl or ethyl.

Reference in the present specification to an aryl group means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, 10 heteroatom for example O, N and/or S, such as pyridyl, pyrrolyl, furanyl and thiophenyl. Preferably, the aryl group comprises phenyl or substituted phenyl.

The alkyl and aryl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 15 substituent. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, alkylamino, dialkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide, heterocyclic groups which may themselves 20 be substituted; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl. Alkyl includes substituted and unsubstituted benzyl. Reference in the present specification to alkoxy and aryloxy groups means alkyl-O- and aryl-O- groups, respectively. Reference to alkoyl and aryloyl groups means alkyl-CO- and aryl-CO-, respectively.

25 Reference in the present specification to heterocyclic groups means groups containing one or more, optionally bridged, rings containing 1 to 6 heteroatoms in total. Each ring in the group may contain 3 to 12, preferably 1 to 6, atoms in total. At least one ring present contains 1 to 2 heteroatoms. Where two or more rings are present they may be fused or 30 unfused. The rings can contain unsaturation. Heteroatoms includes O, S and N. Examples of such heterocyclic groups containing one or more pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuran, pyran, pyronyl, pyridyl, pyrazinyl, pyridazinyl,

piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and
-5 carbolinyl.

References in the present specification to polycyclic groups means a group comprising two or more non-aromatic carbocyclic or heterocyclic rings which may themselves be substituted. Preferably the group contains 2 to 4 fused or non-fused rings, each ring
10 suitably containing 3 to 12 atoms, more suitably 4 to 10, more suitably 5 to 7, and even more suitably 5 to 6 atoms. The definitions of cyclic alkyl and heterocyclic rings given above also apply to the rings in the polycyclic groups.

Reference in the present specification to halogen means a fluorine, chlorine, bromine or
15 iodine radical, preferably fluorine or chlorine radical.

The group Ar comprises a substituted or unsubstituted aryl group, wherein the term "aryl group" and the possible substitution of said group is as defined above. Preferably, Ar is a substituted or unsubstituted phenyl group. Particularly preferred substituents are electron
20 withdrawing groups such as halogen (preferably chlorine or fluorine), trihalomethyl (preferably trifluoromethyl), cyano and nitro groups. Preferably, Ar is phenyl, 3,5-dichloro-phenyl, p-trifluoromethyl-phenyl, p-cyano-phenyl, or p-nitro-phenyl.

R³ is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups.

25

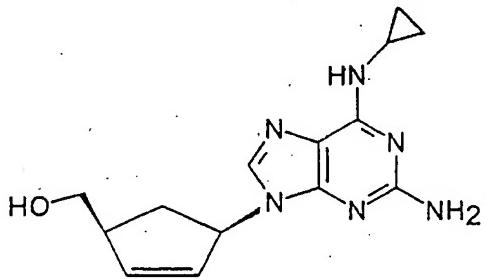
Preferably, R³ is a substituted or unsubstituted alkyl group. Preferably, R³ is a substituted or unsubstituted C₁₋₆ alkyl group, more preferably an ethyl or methyl group.

Preferably, at least one of R¹ and R² is hydrogen. It will be appreciated that if R¹ and R²
30 are different, the carbon atom to which they are bonded is an asymmetric centre. Preferably this carbon atom is chiral. When this carbon atom is chiral, the stereochemistry at this site may be D or L or mixed, with L-stereochemistry being preferred.

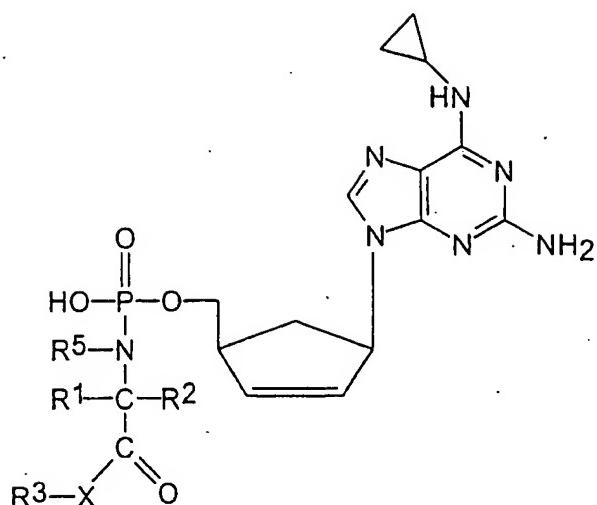
R⁵ and R¹ can be linked to form an alkylene bridge comprising 3 to 4 carbon atoms so as to form a 5- or 6- membered ring. Preferably R⁵ is hydrogen.

It will be appreciated that the group -NH-CHR¹-CO₂R³ corresponds to a carboxy-protected 5 α-amino acid. Preferably, the group R¹ corresponds to the side chain of a naturally occurring amino acid such as Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Cystine, Glycine, Glutamic Acid, Glutamine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine. Preferably, R¹ is Me or PhCH₂ corresponding to the side chain of alanine or phenylalanine, 10 respectively. Preferably, the stereochemistry at the asymmetric centre -CHR¹- corresponds to an L-amino acid.

It is a feature of the aryl ester phosphate compounds of the present invention that they exhibit significantly enhanced anti-viral efficacy in *in vitro* tests, in comparison to their 15 corresponding nucleoside analogue, (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, which is known as Abacavir and which has the following structural formula:



According to a further aspect of the present invention there is provided a compound of 20 formula (II):



wherein R^1 , R^2 , R^3 , R^5 and X are as defined above, or a pharmaceutically acceptable derivative or metabolite thereof. Preferably X is O.

- 5 The intracellular generation of such anti-viral metabolites is an important feature of the invention for several reasons. In cases where the nucleoside is not a good substrate for host nucleotide kinases, activation will be poor and anti-viral efficacy low, even if the triphosphate is an excellent RT inhibitor. In such cases, the generation of the present metabolites may lead to a very significant enhancement in anti-viral action.

10

By "a pharmaceutically acceptable derivatives" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of the present formula or present metabolite. Preferred "pharmaceutically acceptable derivatives" include 15 sodium, succinate, fumarate, glutarate and D-tartrate salts.

By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of the present formula or present metabolite which gives rise to reverse transcriptase inhibition exhibited by the present compounds.

20

According to a further aspect of the present invention there is provided a compound according to the present invention for use in a method of treatment, preferably in the prophylaxis or treatment of viral infection.

According to a further aspect of the present invention there is provided use of a compound according to the present invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection.

5

According to a further aspect of the present invention there is provided a method of prophylaxis or treatment of viral infection comprising administration to a patient in need of such treatment an effective dose of a compound according to the present invention.

- 10 The viral infection may comprise any viral infection such as HIV and herpes virus, including HSV 1 and HSV 2, CMV, VZV, EBV, HAV, HBV, HCV, HDV, HHV6, HHV7, HHV8, papilloma, adenoviruses, rabies and influenza.

- 15 Preferably, the viral infection comprises HIV or HBV infection, more preferably HIV-I or HIV-II. It is a feature of the present invention that the compounds exhibit good activity against HIV-I and HIV-II, and HBV.

- 20 According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of combining a compound of the present invention with a pharmaceutically acceptable excipient.

25

Compounds of the present invention can demonstrate significant stability towards acid-mediated hydrolytic decomposition. The present compounds can thus be particularly suitable for oral administration under typical dosing conditions in humans as they can retain stability under the highly acidic environment of the stomach.

30

As the purine in compounds of formula (I) is a weak base ($pK_a=5.0$) and the compounds of formula (I) demonstrate stability to acids, salts can be formed of compounds of formula (I) with acids, such as carboxlic acids and dicarboxlic acids. Such salts can be stable,

crystalline solids, which can be beneficial in terms of improved shelf-life and ease of handling during manufacture into pharmaceutical compositions. Preferred carboxylic and dicarboxylic acids include malonic, succinic, glutaric, fumaric and tartaric acids. In contrast to the salts of compounds of formula (I), the free bases of compounds of formula 5 (I) can be in a non-crystalline amorphous form which can be hygroscopic.

The P-OH group of compounds of formula (II) is a weak acid and can therefore form monobasic salts with bases to give, for example, sodium, potassium, ammonium, and triethylammonium salts. In compounds of formula (II) when X is OH, dibasic salts can be 10 formed. Such dibasic salts can be in the form of stable solids, which can provide benefits of improved shelf-life and ease of handling during manufacture into pharmaceutical compositions.

Compounds of the present invention can also demonstrate enhanced stability in biological 15 media, for example, in human plasma. The increased half-life of compounds embodying the present invention in media such as human plasma may permit a pharmacokinetic advantage in dosing in humans in need of treatment.

The medicament employed in the present invention can be administered by oral or 20 parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

For oral administration, the compounds of the invention will generally be provided in the 25 form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredients mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, 30 lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating

agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

5 Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredients is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

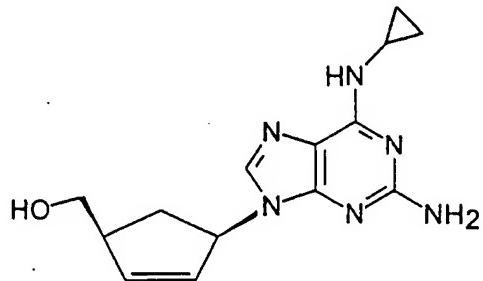
10 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

15 For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention 20 may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

The compounds of the invention may also be presented as liposome formulations.

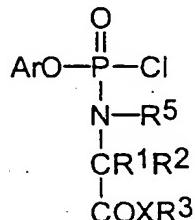
25 In general a suitable dose will be in the range of 0.01 to 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 1.0 mg per kilogram body weight per day. The desired dose is preferably presented once daily, but may be dosed as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout 30 the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

According to a further aspect of the present invention there is provided a process for the preparation of the present compound comprising reaction of a compound of formula



with a compound of formula

5



wherein R^1 , R^2 , R^3 , R^5 and X have the meanings given above.

- 10 The reaction may be carried out under dry conditions at ambient temperature in tetrahydrofuran in the presence of N-methylimidazole, or by using t-butyl magnesium chloride and an excess of the appropriate phosphorochloride reagent.

Compounds embodying the present invention wherein Ar is replaced by H may be
15 prepared from the acid form by treatment of the ester with an aqueous base.

Compounds wherein X is NH or NR^4 can be prepared by treating the acid form ($\text{X} = \text{O}$ and $\text{R}^3 = \text{H}$) with amine.

- 20 The above starting material, (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, is known as Abacavir and may be made by any procedure known in the art, for example by procedures described in European Patent Specification

Number 0434450, PCT Patent Application No. PCT/GB95/02014, and PCT Patent Application No. PCT/EP98/02835, all of which are incorporated by reference thereto.

The invention will now be described with reference to the following Examples. It will be
5 appreciated that what follows is by way of example only and that modifications to detail
may be made whilst still falling within the scope of the invention.

EXPERIMENTAL PROCEDURES

General methods

- 5 The following anhydrous solvents and reagents were bought dry from Aldrich with sure seal stoppers: Dichloromethane (DCM), diethyl ether (Et₂O), tetrahydrofuran (THF), N-methyl imidazole (NMI), methanol (MeOH), dimethylformamide (DMF), pyridine (pyr), dioxane, and tBuMgCl. Triethylamine (NEt₃) was dried by refluxing over CaH₂ for several hours and then distilled off for immediate use.

10

Chromatography

- Thin layer chromatography (tlc) was performed on commercially available Merck Kieselgel 60F₂₅₄ plates and the separated components were visualised using ultra violet light (254nm and 366nm), or by treatment with a 5% ethanolic solution of dodeca-molybdo-phosphoric acid (MPA) followed by heating. Column chromatography was performed using Woelm silica (32-63mm) as the stationary phase.

Spectral Characterisation

20

All NMR spectral data, unless otherwise stated, were obtained in CDCl₃. Proton and Carbon-13 nuclear magnetic resonance were recorded on a Bruker Avance DPX300 spectrometer with operating frequencies of 300MHz and 75MHz respectively. Phosphorous-31 NMR spectra were recorded on a Bruker Avance DPX300 spectrometer

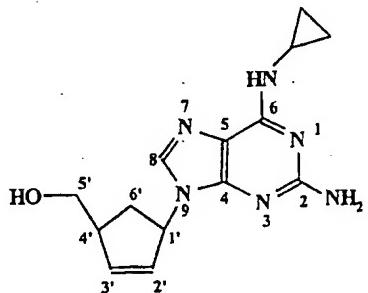
25 operating at 121MHz, and are reported in units of δ relative to 85% phosphoric acid as the external standard, positive shifts are downfield. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal), dd (double of doublets), dt (double of triplets).

30 Low resolution mass spectra were run on a VG Platform II Fisons instrument (Fisons, Altrincham, UK) (atmospheric pressure ionization, electrospray mass spectrometry) in either negative or positive ion mode.

High Performance Liquid Chromatography (HPLC) was performed on an SSODS2 reverse phase column with an eluent of water/acetonitrile. 100% water (0 mins), 20% water (35mins), 20% water (45mins), 100% water (55mins), with a flow rate of 1 ml/min and detection by UV at 254 nm. Standards: acetone (t_R 4.54mins), toluene (t_R 10.21mins). Final products showed purities >99%, with undetectable amounts of the parent nucleoside.

Nomenclature and Numbering of Compounds

IUPAC nomenclature is used where possible, but for ease some compounds are abbreviated. Numbering is by conventional nucleoside numbering.



Standard Procedures

15

For practical purposes, standard procedures are given where applicable.

Standard Procedure 1

To a stirring solution of anhydrous alcohol (10mol eq) was added thionyl chloride (2mol eq) dropwise at 0°C, and the resulting solution stirred for 1hr. Upon rising to room temperature, the appropriate amino acid (1mol eq) was added and the reaction heated at reflux for 6-16hrs. Removal of the solvent and recrystallisation from methanol:ether gave the amino ester hydrochloride salts.

Standard Procedure 2

The appropriate amino acid (1mol eq), para-toluene sulfonic acid (1.1mol eq) and the appropriate alcohol (1mol eq) were heated under reflux in toluene (100ml), under Dean 5 and Stark conditions, for 6-16hrs. On cooling to room temperature the solvent was removed under reduced pressure to give an oil. This was solubilised in dichloromethane (50ml) and washed with 10% K₂CO₃ (50ml), and water (50ml), filtered and the filtrate reduced to dryness to give an oil. This was solubilised in the minimum amount of acetone and neutralised with 2M HCl, and then lyophilised to give the amino acid ester 10 hydrochloride salts.

Standard procedure 3

Phenyl dichlorophosphate (1mol eq) and the appropriate amino acid ester hydrochloride 15 salt (1mol eq) were suspended in anhydrous dichloromethane (30-60ml). Anhydrous triethylamine (2mol eq) in anhydrous dichloromethane (30ml) was added dropwise at -80°C, and the reaction left to rise to room temperature overnight. The solvent was removed under reduced pressure, and under nitrogen, to give white solids. This was washed with anhydrous ether (2x25ml), filtered and the filtrate reduced to dryness to give the products 20 as crude oils. These were stored in anhydrous THF and used without any further purification.

Standard Procedure 4

25 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (1mol eq) was dried by azeotroping with anhydrous pyridine (3x5ml), and then suspended in anhydrous THF (5-30ml). To the suspension was added tBuMgCl (1-2mol eq, 1.0M solution in THF) dropwise, and the resulting suspension stirred for 10mins. The phosphorochloridate species (3mol eq, solution in THF) was then added dropwise and the 30 resulting solution stirred at room temperature for 24-96hrs. The reaction was then quenched by the addition of sat.NH₄Cl (0.1ml), and after 10mins the solvent was removed under reduced pressure. The crude product was purified by silica column chromatography.

L-Alanine methyl ester hydrochloride.**C₄H₁₀O₂N₁Cl₁, MW=139.38.**

This was synthesised according to Standard Procedure 1, using anhydrous methanol
 5 (34ml, 0.84mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (2.87g, 36.7%).

¹H NMR (D₂O): δ 4.07-4.00 (1H,q,CH,J=7.22Hz), 3.83 (3H,s,OCH₃), 1.39-1.37 (3H,t,CH₃).

¹³C NMR (D₂O): δ 171.5 (CO), 53.9 (O CH₃), 49.1 (CH), 15.4 (CH₃).

10

Phenyl-(methoxy-L-alaninyl)-phosphorochloridate.**C₁₀H₁₃O₄N₁Cl₁P₁, MW=277.65.**

This was synthesised according to Standard Procedure 3, using L-Alanine methyl ester hydrochloride (2.0g, 14.34mmol), phenyl phosphorodichloridate (3.02g, 2.14ml, 15 14.34mmol) and anhydrous triethylamine (2.90g, 4.0ml, 28.68mmol). The product (3.91g, 98.2%) was isolated as a colourless crude oil which was stored in anhydrous THF (40ml) to give a 0.47M solution.

³¹P NMR: δ 9.28, 8.97 (1:1).

¹H NMR: δ 7.39-7.34 (2H,m,'o'-Ph), 7.29-7.20 (3H,m,'m'+'p'-Ph), 4.49-4.37 (1H,q,NHala), 4.27-4.09 (1H,m,CHala), 3.78 (3H,d,OCH₃), 1.52-1.49 (3H,dd,CH₃).
 20 ¹³C NMR: 173.6 (CO), 150.1 ('ipso'-Ph), 130.25 ('m'-Ph), 126.4 ('p'-Ph), 120.9 ('o'-Ph), 53.2 (OCH₃), 51.0 (CH), 20.9 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
 25 O-[phenyl-(methoxy-L-alaninyl)]-phosphate. Cf1490.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (500mg, 1.75mmol), tBuMgCl (1.0M solution in THF) (1.75ml, 1.75mmol) and phenyl-(methoxy-L-alaninyl)-tBuMgCl (0.47M solution in THF) (11.17ml, 5.24mmol), in THF (30ml) and stirring at room temperature for 70hrs. The crude product was purified by column chromatography eluting with 3% MeOH in DCM and then 2% MeOH in DCM to give the product as a white foam (442mg, 48%).

³¹P NMR (MeOH-d₄): δ 3.97, 3.88.

¹H NMR: δ 7.41 (1H,d,C8), 7.24-7.19 (2H,m,'o'-Ph), 7.13-7.03 (3H,m,'m+'p'-Ph), 6.08 (1H,bs,NH), 5.98 (1H,q,H2'), 5.78 (t,H3'), 5.44 (1H,t,H1'); 5.09 (2H,bs,NH₂), 4.22-4.02 (3H,m,NHala+H5'), 3.99-3.87 (1H,m,CHala), 3.59 (3H,t,OCH₃), 3.05 (1H,d,H4'), 2.92 (1H,bs,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.53 (1H,m,1of H6'), 1.30-1.25 (3H,t,CH₃ala), 0.78-0.71 (2H,q,2H of CH₂cPr), 0.54-0.49 (2H,t,2H of CH₂cPr).

¹³C NMR: δ 174.6 (CO), 160.3 (C2), 156.6 (C4), 151.3 (C6), 151.1 ('ipso'-Ph), 136.8 (C8), 135.9 (C2'), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.5 ('o'-Ph), 115.0 (C5), 69.2 (C5'), 59.2 (C1'), 52.8 (OCH₃), 50.5 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 21.2 (CH₃ala), 7.7 (CH₂cPr).

MS ES⁺ : m/z 527.86 (100%) (M)⁺, 546.84 (M+K)⁺.

MS FAB: For C₂₄H₃₁O₅N₇P, requires 528.212431, found 528.213848.

HPLC: t_R 30:33 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3328.6 (N-Hstr.), 2922.1, 2862.9 (C-Hstr.), 1734.4 (C=Ostr.), 1590.9 (aromatic C-Cstr.), 1462.9 (C-Hdef.), 1376.8 (-CH₃sym.def.), 1207.1 (P-O-aryl), 1154.0 (C-Ostr.), 1027.7 (P-O-alkyl), 933.4 (olefinic C-Hdef.), 721.8 (monosub.aromatic C-Hdef.).

Phenyl-(methoxy-D-alaninyl)-phosphorochloridate.

20 C₁₀H₁₃O₄N₁Cl₁P₁, MW=277.65.

This was synthesised according to Standard Procedure 3, using D-alanine methyl ester hydrochloride (1.0g, 7.17mmol), PhOP(O)Cl₂ (1.51g, 1.07ml; 7.17mmol) and NEt₃ (1.45g, 2.0ml, 14.0mmol) to yield 1.66g (83.4%) of crude product that was stored in anhydrous THF (10ml), to give a 0.60mmol/ml solution that was used without further purification.

25 ³¹P NMR: δ 9.38, 9.18 (1:1).

¹H NMR: δ 7.39-7.30 (2H,t,'o'-Ph), 7.29-7.09 (3H,m,'m+'p'-Ph), 4.85-4.80 (1H,d,NHala), 4.19-4.11 (1H,m,CHala), 3.75 (3H,d,OCH₃), 1.52-1.49 (3H,dd,CH₃ala).

¹³C NMR: δ 173.6 (CO), 150.1 ('ipso'-Ph), 130.3 ('o'-Ph), 126.4 ('p'-Ph), 120.9 ('m'-Ph), 53.2 (OCH₃), 50.9 (CHala), 21.0 (CH₃ala).

30

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-D-alaninyl)]-phosphate. Cf1583.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (400mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (2.1ml, 2.1mmol), and phenyl-(methoxy-D-alaninyl)-phosphorochloridate (0.6M solution in THF) (7.0ml, 4.19mmol) in THF (25ml) stirring at room temperature for 36hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then 2.5% MeOH in CHCl₃ to give the product as a white foam (318.6mg, 43.2%).

³¹P NMR: δ 3.93, 3.70.

¹H NMR: δ 7.56+7.51 (1H,d,H8), 7.37-7.32 (2H,m,'o'-Ph), 7.29 (1H,d,'p'-Ph), 7.25-7.15 (2H,m,'m'-Ph), 6.10 (1H,t,J=5.28Hz,H2'), 6.03 (1H,bs,NHcPr), 5.94-5.89 (1H,m,H3'), 5.54 (1H,bs,H1'), 5.01 (2H,bs,NH₂), 4.26-3.83 (4H,m,CHala,NHala+H5'), 3.72 (3H,d,OCH₃), 3.18 (1H,s,CHcPr), 3.02 (1H,bs,H4'), 2.86-2.75 (1H,m,1 of H6'), 1.78-1.64 (1H,m,1 of H6'), 1.39-1.36 (3H,dd,CH₃ala), 0.90-0.83 (2H,q,J=6.13Hz,2H of CH₂cPr), 0.63 (2H,bs, 2H of CH₂cPr).

13C NMR: δ 174.5 (CO), 160.3 (C2), 156.6 (C4) 151.2 (C6), 151.0 ('ipso'-Ph), 136.8 (C2'), 136.1 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.3 ('p'-Ph), 120.5 ('o'-Ph), 115.2 (C5), 69.3 (C5'), 59.3 (C1'), 52.9 (CHala), 50.5 (OCH₃), 46.0 (C4'), 34.9 (C6'), 24.1 (CHcPr), 21.4 (CH₃ala), 7.8 (CH₂cPr).

MS ES⁺ : m/z 527.86 (100%) (M)⁺, 546.84 (M+K)⁺.

MS FAB: For C₂₄H₃₁O₅N₇P requires 528.212431, found 528.211505.
 HPLC: t_R 29.807 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
 IR: 3333.6 (N-Hstr.), 2923.4, 2853.4 (C-Hstr.), 1734.1 (C=Ostr.), 1591.1 (aromatic C-Cstr.), 1458.3 (C-Hdef.), 1376.7 (-CH₃sym.def.), 1208.3 (P-O-aryl), 1153.3 (C-Ostr.), 1026.9 (P-O-alkyl), 931.9 (olefinic C-Hdef.), 721.6 (monosub.aromatic C-Hdef.).

Phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate.

C₁₆H₁₇O₄N₁Cl₁P₁, MW=353.74.

This was synthesised according to Standard Procedure 3, using L-phenylalanine methyl ester (1.0g, 4.64mmol), PhOP(O)Cl₂ (0.98g, 0.70ml, 4.64mmol) and NEt₃ (0.94g, 1.30ml, 9.28mmol) to yield 1.45g (88.4%) of crude product as an oil that was stored in anhydrous THF (10ml), to give a 0.41mmol/ml solution that was used without further purification.

³¹P NMR: δ 9.37, 9.23 (1:1).

¹H NMR: δ 7.60-7.16 (10H,m,2xPh), 4.70-4.49 (1H,m,CHala), 4.38-4.16 (1H,m,NHala), 3.89 (3H,d,OCH₃), 3.23 (2H,m,CH₂Ph).

- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
- 5 O-[phenyl-(methoxy-L-phenylalaninyl)]-phosphate. Cf1585.
 $C_{31}H_{34}O_5N_7P_1$, MW=603.6.
- This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate (0.41M solution in THF) (7.66ml, 3.14mmol) in THF (20ml) stirring at room temperature for 48hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then 2.5% MeOH in CHCl₃ to give the product as a white foam (272.9mg, 43.15%).
- ³¹P NMR: δ 3.91, 3.80.
- 15 ¹H NMR: δ 7.47+7.43 (1H,d,H8), 7.31-7.06 (10H,m,2xPh), 6.25 (1H,d,NHcPr), 6.00-5.95 (1H,q,H2'), 5.87-5.81 (1H,t,H3'), 5.49 (1H,s,H1'), 5.19 (2H,bs,NH₂), 4.31-3.92 (4H,m,CHala,NHala+H5'), 3.64 (3H,d,OCH₃), 3.02-2.89 (4H,m,CH₂Ph,CHcPr+H4'), 2.78-2.63 (1H,m,1 of H6'), 1.63-1.49 (1H,m,1 of H6'), 0.86-0.80 (2H,q,J=6.24Hz,2H of CH₂cPr), 0.60 (2H,d,2H of CH₂cPr).
- 20 ¹³C NMR: δ 174.3 (CO), 161.5 (C2), 157.7 (C4), 152.4 (C6) 152.1 ('ipso'-OPh), 137.7 ('ipso'-Bn), 137.1 (C2'), 136.9 (C8), 132.4 (C3'), 130.9 ('o'+m'-Bn), 129.9 ('m'-OPh), 128.4 ('p'-Bn), 126.2 ('p'-OPh), 121.5 ('o'-OPh), 116.1 (C5), 70.1 (C5'), 60.1 (C1'), 57.2 (CHala), 53.6 (OCH₃), 46.9 (C6'), 41.7 (C4'), 35.9 (CH₂Ph), 25.1 (CHcPr), 8.7 (CH₂cPr).
MS ES⁺ : m/z 603.8 (100%, M⁺), 604.8 (35%, M+H⁺), 625.7 (15%, M+Na⁺).
- 25 MS FAB: For $C_{31}H_{34}O_5N_7P$ requires 604.243731, found 604.242585.
HPLC: t_R 34.707, 35.020 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3331.7 (N-Hstr.), 3007.2, 2952.2 (C-Hstr.), 1741.1 (C=Ostr.), 1595.6, 1487.7 (aromatic C-Cstr.), 1455.0 (C-Hdef.), 1393.9 (-CH₃sym.def.), 1252.5 (P=O), 1214.3 (P-O-aryl),
- 30 1125.3 (C-Ostr.), 1025.6 (P-O-alkyl), 935.8 (olefinic C-Hdef.), 754.8 (monosub.aromatic C-Hdef.).

Phenyl-(methoxyglycanyl)-phosphorochloridate .



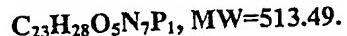
This was synthesised according to Standard Procedure 3, using glycine methyl ester (1.5g, 11.9mmol), PhOP(O)Cl₂ (2.52g, 1.79ml, 11.9mmol) and NEt₃ (2.42g, 3.33ml, 23.9mmol) to yield 3.07g (97.15%) of crude product as an oil that was stored in anhydrous THF (15ml), to give a 0.774mmol/ml solution that was used without further purification.

5 ³¹P NMR: δ 10.43.

1H NMR: δ 7.43-7.38 (2H,m,'o'-Ph), 7.31-7.25 (3H,m,'m'+p'-Ph), 4.67 (1H,bs,NHala), 3.94 (2H,dd,CH₂), 3.83 (3H,s,OCH₃).

10 ¹³C NMR: δ 170.4 (CO), 150.1 ('ipso'-Ph), 130.2 ('m'-Ph), 126.4 ('p'-Ph), 120.8 ('o'-Ph), 53.1 (OCH₃), 43.4 (CH₂).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl-(methoxy-glyciny)]-phosphate. Cf1588.



15 This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-glyciny)-phosphorochloridate (0.774M solution in THF) (4.06ml, 3.14mmol) in THF (20ml) stirring at room temperature for 96hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then with 2.5% MeOH in CHCl₃ to give the product as a white foam (82.6mg, 15.4%).

20 ³¹P NMR: δ 4.79, 4.67 (1:1).
1H NMR: δ 7.40+7.36 (1H,d,H8), 7.24-7.19 (2H,t,'o'-Ph), 7.15-7.10 (2H,t,'m'-Ph), 7.07-7.02 (1H,t,'p'-Ph), 6.00-5.96 (2H,m,H2'+NHcPr), 5.80-5.76 (1H,m,H3'), 5.45-5.41 (1H,t,H1'), 4.99 (2H,bs,NH₂), 4.14-4.00 (3H,m,NHala+H5'), 3.62 (3H,s,OCH₃), 3.03 (1H,d,H4'), 2.91 (1H,d,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.51 (1H,m,1of H6'), 1.45-1.43 (6H,t,2xCH₃), 0.78-0.71 (2H,q,2H of CH₂cPr), 0.54-0.49 (2H,t,2H of CH₂cPr).

25 ¹³C NMR: δ 172.1 (CO), 160.2 (C2), 156.6 (C4), 152.0 (C6), 151.7 ('ipso'-Ph), 137.7 (C8), 137.1 (C2'), 132.0 (C3'), 130.8 ('m'-Ph), 126.0 ('p'-Ph), 121.2 ('o'-Ph), 115.5 (C5), 69.9 (C5'), 60.0 (C1'), 53.5 (OCH₃), 46.7 (C4'), 43.9 (CH₂), 35.4 (C6'), 25.0 (CHcPr), 8.5 (CH₂cPr).

30 MS ES⁺: m/z 513.9 (100%, M⁺), 514.8 (25%, M+H⁺), 535.8 (40%, M+Na⁺).

MS FAB: For $C_{23}H_{29}O_5N_7P$ requires 514.196781, found 514.195321.

HPLC: t_R 28.419 (99.9%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3342.0 (N-Hstr.), 1749.8 (C=Ostr.), 1596.2, 1488.4 (aromatic C-Cstr.), 1451.9 (C-Hdef.), 1394.7 (-CH₃sym.def.), 1259.6 (P=O), 1212.1 (P-O-aryl), 1151.6 (C-Ostr.), 1026.8 (P-O-alkyl), 937.8 (olefinic C-Hdef.), 760.7 (monosub.aromatic C-Hdef.).

Methyl-2-amino-2-methylpropanoate hydrochloride.

C₅H₁₂O₂N₁Cl₁, MW=153.61.

10 This was synthesised according to **Standard Procedure 1**, using 2-amino-isobutyric acid (4g, 0.039mol) with thionyl chloride (5.66ml, 0.078mol) and anhydrous methanol (23.5ml, 0.58mol). This gave the product as a white solid (5.805g, 97.4%).

¹H NMR (DMSO): δ 8.85 (3H,s,NH₃⁺Cl⁻), 3.72 (3H,s,OMe), 1.48 (6H,s,2xMe).

¹³C NMR (DMSO): δ 172.8 (COOMe), 56.6 (OMe), 53.9 (CMe₂), 24.1 (2xMe).

15 MS ES⁺ : m/z 117.71 M+H⁺, 142.88 M+Na⁺.

Phenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate.

C₁₁H₁₅O₄N₁Cl₁P₁, MW=291.67.

This was synthesised according to **Standard Procedure 3**, using 2-amino-isobutyrate methyl ester hydrochloride (1.0g, 6.51mmol), PhOP(O)Cl₂ (1.37g, 0.97ml, 6.51mmol) and NEt₃ (1.32g, 1.18ml, 13.02mmol), to yield 1.73g (91%) of the crude product as an oil. This was stored in anhydrous THF (10ml) to give a solution of 0.593mmol/ml, and used without further purification.

³¹P NMR: δ 6.86.

25 ¹H NMR: δ 7.43-7.38 (2H,t,'o'-Ph), 7.32-7.21 (3H,m,'m '+'p'-Ph), 4.84 (1H,d,NHala), 3.83 (3H,s,OCH₃), 1.72 (6H,d,2xCH₃).

¹³C NMR: δ 175.7 (CO), 150.3 ('ipso'-Ph), 130.3 ('m'-Ph), 126.3 ('p'-Ph), 121.0 ('o'-Ph), 58.8 (OCH₃), 53.6 (C[CH₃]₂), 27.3 + 27.0 (2xCH₃).

30 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

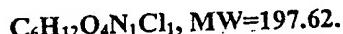
O-[phenyl-(methoxy-a,adimethylglycinyl)]-phosphate. Cf1584.

C₂₅H₃₂O₅N₇P₁, MW=542.23.

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-dimethylglycinyl)-phosphorochloridate (0.59M solution in THF) (5.3ml, 3.14mmol) in 5 THF (20ml) stirring at room temperature for 96hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then with 2.5% MeOH in CHCl₃ to give the product as a white foam (193.7mg, 34.14%).

- ³¹P NMR: δ 2.49.
- ¹H NMR: δ 7.40-7.36 (1H,d,H8), 7.24-7.19 (2H,t,'o'-Ph), 7.15-7.10 (2H,t,'m'-Ph), 7.07-10 7.02 (1H,t,'p'-Ph), 6.00-5.96 (2H,m,H2'+NHcPr), 5.80-5.76 (1H,m,H3'), 5.45-5.41 (1H,t,H1'), 4.99 (2H,bs,NH₂), 4.14-4.00 (3H,m,NHala+H5'), 3.62 (3H,s,OCH₃), 3.03 (1H,d, H4'), 2.91 (1H,d,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.51 (1H,m,1of H6'), 1.45-1.43 (6H,t,2xCH₃), 0.78-0.71 (2H,q,2H of CH₂cPr), 0.54-0.49 (2H,t,2H of CH₂cycl.).
- MS ES⁺ : m/z 541.9 (100%, M⁺), 563.8 (30%, M+Na⁺).
- 15 MS FAB: For C₂₅H₃₃O₅N₇P requires 542.228081, found 542.228428.
- HPLC: t_R 28.347 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
- IR: 3346.0 (N-Hstr.), 2923.0, 2853.5 (C-Hstr.), 1734.0 (C=Ostr.), 1590.2 (aromatic C-Cstr.), 1458.4 (C-Hdef.), 1376.8 (-CH₃sym.def.), 1261.3 (P=O), 1152.7 (C-Ostr.), 1028.0 (P-O-alkyl), 936.0 (olefinic C-Hdef.), 721.7 (monosub.aromatic C-Hdef.).

L-Aspartic acid dimethyl ester hydrochloride.



This was synthesised according to Standard Procedure 1, using L-asparagine (2.5g, 25 0.019mol) with thionyl chloride (3.67ml, 0.042mol) and anhydrous methanol (12.86ml, 0.32mol). This gave L-aspartic acid dimethyl ester hydrochloride in 3.70g, 99% yield.

¹H NMR (MeOH-d₄): δ 4.53-4.50 (1H,t,CH), 3.94 (3H,s,OCH₃), 3.85 (3H,s,OCH₃), 3.18 (2H,d,CH₂).

¹³C NMR (MeOH-d₄): δ 170.4, 168.4 (CO), 53.0+52.0 (2xOMe), 49.4 (CH), 33.8 (CH₂).

Phenyl-(dimethoxy-L-aspartyl)-phosphorochloridate.



This was synthesised according to Standard Procedure 3, using L-Aspartic acid dimethyl ester (1.0g, 5.04mmol), PhOP(O)Cl₂ (1.06g, 0.75ml, 5.04mmol) and NEt₃ (1.02g, 1.40ml, 10.1mmol) to yield 0.55g (32.4%) of crude product as an oil that was stored in anhydrous THF (5ml), to give a 0.33mmol/ml solution that was used without further purification.

5 ³¹P NMR: δ 9.74, 9.59 (1:1).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-[phenyl-(L-aspartic acid dimethyl ester)]-phosphate. Cf1589.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

10 This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (250mg, 0.87mol), tBuMgCl (1.0M solution in THF) (0.87ml, 0.87mmol) and phenyl-(L-aspartic acid dimethyl ester)-phosphorochloridate (0.50M solution in THF) (5.20ml, 2.62mmol) in THF (15ml) and stirring at room temperature for 48hrs. The crude product was purified by 15 eluting with 2.5% MeOH in CHCl₃ (x2) to give the product as a pale yellow foam (163.5mg, 32.0%).

³¹P NMR: δ 4.19, 3.76 (1:1).

¹H NMR: δ 7.40 (1H,d,H8), 7.24-7.19 (2H,t,'o'-Ph), 7.12-7.03 (3H,m,'m'+'p'-Ph), 6.05-5.95 (2H,m,H2'+NHcPr), 5.79 (1H,d,H3'), 5.44 (1H,s,H1'), 5.02 (2H,bs,NH₂), 4.38-4.07

20 (4H,m,H5',NHala+CHala), 3.61 (3H,s,OCH₃), 3.54 (3H,d,OCH₃), 3.05-2.52 (5H,m,CH₂aa,H4',CHcPr,+1of H6'), 1.64-1.52 (1H,m,1of H6'), 0.77-0.73 (2H,t,J=5.49Hz,2Hof CH₂cPr), 0.51 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 173.3 (CO), 172.4 (CO), 161.5 (C2), 157.7 (C4), 152.3 (C8), 152.1 ('ipso'-Ph), 137.8 (C2'), 137.0 (C6), 132.6 (C3'), 131.1 ('m'-Ph), 126.4 ('p'-Ph), 121.6 ('o'-Ph),

25 116.2 (C5), 70.5 (C5'), 60.3 (C1'), 54.3 (OCH₃), 53.5 (OCH₃), 52.6 (CHala), 47.1 (C4'), 39.7 (CH₂ala), 36.0 (C6'), 25.1 (CHcPr), 8.8 (CH₂cPr).

MS ES⁺: m/z 585.8 (100%, M⁺), 607.7 (30%, M+Na⁺).

MS FAB: For C₂₆H₃₃O₅N₇P requires 586.217910, found 586.217510.

HPLC: t_R 29.261 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins),

30 100% water (55mins)).

IR: 3347.5 (N-Hstr.), 2850.7 (C-Hstr.), 1739.9 (C=Ostr.), 1596.1 (aromatic C-Cstr.), 1461.9 (C-Hdef.), 1376.6 (-CH₃sym.def.), 1262.4 (P=O), 1211.2 (P-O-aryl), 1158.3 (C-

Ostr.), 1027.0 (P-O-alkyl), 935.6 (olefinic C-Hdef.), 761.5, 722.0 (monosub.aromatic C-Hdef.).

3-cyclohexyl-L-alanine methyl ester hydrochloride salt

5 C₉H₁₉N₁O₂Cl₁, MW=221.75

This was synthesised according to Standard Procedure 1, using 3-cyclohexyl-L-alanine (3.0g, 17.5mmol), methanol (30ml), and thionyl chloride (2.56ml, 35mmol). The product was isolated as a white solid (3.23g, 83.9%).

10 ¹H NMR (MeOH-d₄): δ 4.12-4.07 (3H,t,CHala), 3.85 (3H,s,OCH₃), 1.74-1.68 (6H,m,CH₂+o-CH₂), 1.56-1.43 (1H,m,CH), 1.36-1.15 (4H,m,m-CH₂), 1.05-0.90 (2H,q,p-CH₂).
¹³C NMR: δ 170.15 (CO), 52.7 (OCH₃), 50.8 (CHala), 38.2 (CH₂), 33.6 (CH), 33.0+32.7 (2xCH₂-o), 26.3 (p-CH₂), 26.0+25.9 (2xCH₂-m).

15 Phenyl-(methoxy-3-cyclohexyl-L-alaninyl)-phosphorochloridate

C₁₆H₂₃N₁O₄P₁Cl₁, MW=359.82

This was synthesised according to Standard Procedure 3, using 3-Cyclohexyl-L-alanine methyl ester hydrochloride salt (0.7g, 316mmol), PhOP(O)Cl₂ (0.47ml, 3.16mmol), triethylamine (0.88ml, 6.31mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (1.18g, 100%), which was stored in THF (7ml) to give a 0.45M solution.

³¹P NMR: δ 9.79, 9.49 (1:1).
¹H NMR: δ 7.49-7.43 (2H,m,'o'-Ph), 7.37-7.19 (3H,m,'m'+p'-Ph), 4.46-4.35 (1H,q,NHala), 4.32-4.20 (1H,m,CHala), 3.88-3.85 (3H,dd,OCH₃), 1.94-1.90 (1H,d,CHcHx), 1.76-1.60

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-Phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphate. CfI 709.**

C₃₀H₄₀N₇O₅P₁, MW=609.66

30 This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (150mg, 0.52mmol), tBuMgCl (1.05ml, 1.05mmol, of a 1.0M solution in THF), in THF (4ml) and phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphorochloridate (3.5ml, 1.57mmol, of a 0.45M

solution in THF), at room temperature for 24hrs. After 24hrs, additional phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphorochloride (2.5ml, 1.12mmol, of a 0.45M solution in THF) was added and the reaction stirred for another 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃, and then 2.5% MeOH in CHCl₃ to give the pure
5 product as a pale yellow foamy solid (79.6mg, 24.9%).

- ³¹P NMR: δ 4.14, 3.98 (1:1).
- ¹H NMR: δ 7.50 (1H,d,H8), 7.34-7.13 (5H,t,OPh), 6.20 (1H,s,NHcPr), 6.08 (1H,t,H2'),
5.89 (1H,q,H3'), 5.53 (1H,bs,H1'), 5.16 (2H,bs,NH₂), 4.24-3.84 (4H,m,H5',NHala+CHala), 3.66 (3H,s,OCH₃), 3.34 (1H,bs,), 3.11 (1H,d,), 3.03 (1H,bs,),
10 2.84-2.72 (1H,m,1of H6'), 1.98-1.36 (8H,m,), 1.11 (3H,bs,), 0.89-0.83 (4H,m,2Hof
cPr+CH₂-'p'), 0.63 (2H,d,2Hof cPr).
- ¹³C NMR: δ 174.8C(=O) 160.2 (C2), 156.5 (C4), 151.3 (C6), 151.2 ('ipso'-Ph), 136.8 (C2'),
135.9 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.5 ('o'-Ph), 115.1 (C5), 69.4
(C5'), 59.3 (C1'), 52.7 (CHala), 46.1 (C4'), 42.5 (CH₂), 34.9 (C6'), 33.8 (CHcHx), 32.7
15 (CH₂-'o'), 26.7 (CH₂-'m'), 26.4 (CH₂-'p'), 24.2 (CHcPr), 7.8 (CH₂cPr).
- MS ES⁺: m/z 610.3 (40%, M⁺), 632.3 (100%, M+Na⁺), 633.3 (25%, M+H+Na⁺).
- MS FAB: For C₃₀H₄₀O₅N₇NaP requires 632.2726, found 632.2727.
- HPLC: t_R 42.154 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins),
100% water (55mins)).

20

- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-(L-alaninyl)-phosphate diammonium salt. Cf1540.**
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-alaninyl)]-phosphate (125mg, 0.24mmol) was stirred in H₂O:NEt₃
25 (10ml, 1:1 v/v), at 25-35°C for 5hrs. The reaction mixture was extracted with DCM
(8x20ml), and the aqueous layer reduced to dryness. The resulting solid was solubilised in
isopropanol and purified by flash column chromatography, gradient eluting with i-
PrOH:H₂O:NH₃ (11:1:1 to 9:1:2). The appropriate fractions were reduced to dryness and
freeze dried to give the pure product as a white foamy solid (106mg, 95%).
- 30 ³¹P NMR (D₂O):- δ 8.62 (s).
- ¹H NMR (D₂O):- δ 7.79 (1H,s,H8), 6.08 (1H,d,H2'), 5.77 (1H,d,H3'), 5.35 (1H,t,H1'),
3.71-3.58 (2H,m,H5'), 3.41-3.32 (1H,m,CHa.a), 3.02-2.94 (1H,m,NHCH), 2.70-2.59

(2H,m,H4'+1 of CH₂), 1.57-1.49 (1H,dt,1 of CH₂), 1.10 (3H,d,CH₃), 0.83-0.76 (2H,q,1 of CH₂cyclo.), 0.61-0.56 (2H,q,1 of CH₂cyclo.).

MS ES⁺ : m/z 437.9 (100%, M⁺).

MS FAB: calculated m/z 438.165481, found m/z 438.163790.

5

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(D-alaninyl)-phosphate diammonium salt.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-D-alaninyl)]-phosphate (100mg, 0.19mmol) was stirred in H₂O:N_{Et}₃ (8ml, 1:1 v/v), for 16hrs. The reaction mixture was extracted with DCM (5x20ml), and the aqueous layer reduced to dryness. The resulting solid was solubilised in isopropanol and purified by flash column chromatography, gradient eluting with i-PrOH:H₂O:NH₃ (11:1:1 to 9:1:2). The appropriate fractions were reduced to dryness and freeze dried to give the pure product as a white foamy solid (88%).

15 ³¹P NMR (MeOH-d₄):- δ 7.81 (s).

¹H NMR:- δ 7.74 (1H,s,H8), 6.12 (1H,d,J=5.53Hz,H2'), 5.78 (1H,t,H3'), 5.44 (1H,d,J=6.21Hz,H1'), 3.74 (2H,t,J=5.42Hz,H5'), 3.70-3.60 (1H,m,CHala), 3.01 (1H,bs,H4'), 2.84 (1H,d,J=3.28Hz,CHcPr), 2.73-2.63 (1H,dt,J=8.66Hz+5.17Hz,1of H6'), 1.67-1.58 (1H,m,1 of CH₂), 1.21 (3H,d,J=7.01Hz,CH₃ala), 0.79-0.73 (2H,q,J=6.68Hz,2H 20 of CH₂cPr), 0.53 (2H,t,2H of CH₂cPr).

¹³C NMR: δ 179.8 (CO), 161.2 (C2), 157.1 (C4), 151.1 (C6), 139.5 (C2'), 137.8 (C8), 130.7 (C3'), 114.6 (C5), 68.0 (C5'), 60.5 (C1'), 51.9 (CHala), 47.6 (C4'), 35.9 (C6'), 24.4 (CHcPr), 21.7 (CH₃ala), 7.6 (CH₂cPr).

MS ES⁺ : m/z 437.9 (100%, M⁺).

25 MS FAB: calculated m/z 438.165481, found m/z 438.167842.

Phenyl-(ethoxy-L-alaninyl)-phosphorochloridate.

C₁₁H₁₅O₄N₁Cl₁P₁, MW=291.67.

This was synthesised according to Standard Procedure 3, using L-Alanine ethyl ester hydrochloride (1.0g, 6.51mmol), PhOP(O)Cl₂ (1.37g, 0.97ml, 6.51mmol) and N_{Et}₃ (1.32g, 1.81ml, 13.0mmol) to yield 1.85g (97.4%) of crude product as an oil that was stored in anhydrous THF (10ml), to give a 0.63mmol/ml solution that was used without further purification.

³¹P NMR: δ 9.41, 9.16 (1:1).

¹H NMR: δ 7.42-7.35 (2H,dd, 'o'-Ph), 7.31-7.25 (3H,m, 'm'+'p'-Ph), 4.71 (1H,d,NHala), 4.31-4.13 (3H,m,OCH₂+CHala), 1.55-1.52 (3H,dd,OCH₂CH₃), 1.33-1.30 (3H,dd,CH₃ala).

¹³C NMR: δ 173.1 (CO), 150.2 ('ipso'-Ph), 130.3 ('m'-Ph), 126.4 ('p'-Ph), 120.9 ('o'-Ph), 62.3 (OCH₂), 51.0 (CHala), 20.9 (CH₂CH₃), 14.5 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-[phenyl-(ethoxy-L-alaniny)]-phosphate. Cf1587.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

- 10 This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol), and phenyl-(ethoxy-L-alaniny)-phosphorochloridate (0.49M solution in THF) (6.45ml, 3.14mmol) in anhydrous THF (20ml), and stirring at room temperature for 24hrs. The crude product was purified by 15 column chromatography eluting with 2.5% MeOH in CHCl₃ to give the product as a pale yellow foam (290mg, 51.1%).

³¹P NMR: δ 4.04, 3.96 (1:1).

- 1 H NMR: δ 7.39 (1H,d,J=7.56Hz,H8), 7.23-7.18 (2H,t,J=7.90Hz,'o'-Ph), 7.12-7.10 (2H,t,'m'-Ph), 7.06-7.01 (1H,t,J=7.13Hz,'p'-Ph), 6.18 (1H,bs,NHcPr), 5.97-5.95 (1H,t,H2'), 5.79-5.75 (1H,t,J=5.55Hz,H3'), 5.43 (1H,s,H1'), 5.13 (2H,bs,NH₂), 4.30-4.14 (1H,m,NHala), 4.06-4.00 (4H,m,H5'+OCH₂), 3.96-3.84 (1H,m,CHala), 3.03 (1H,d,J=5.74Hz,H4'), 2.92 (1H,bs,CHcPr), 2.71-2.61 (1H,m,1of H6'), 1.60-1.51 (1H,m,1of H6'), 1.29-1.24 (3H,t,J=6.64Hz,CH₃ala), 1.18-1.11 (3H,m,CH₂CH₃), 0.75-0.71 (2H,q,J=6.76Hz,2H of CH₂cPr), 0.50 (2H,bs,2H of CH₂cPr).

- 25 ¹³C NMR: δ 173.35 (CO), 159.8 (C2), 156.0 (C4), 150.6 (C6) 150.4('ipso'-Ph), 136.1 (C2'), 135.1 (C8), 130.8 (C3'), 129.3 ('m'-Ph), 124.5 ('p'-Ph), 119.8 ('o'-Ph), 114.4 (C5), 68.6 (C5'), 61.2 (OCH₂), 58.5 (C1'), 50.0 (CHala), 45.3 (C4'), 34.3 (C6'), 23.4 (CHcPr), 20.6 (CH₃ala), 13.8 (CH₂CH₃), 7.0 (CH₂cPr).

MS ES⁺: m/z 541.9 (100%, M⁺), 546.84 (28%, M+H⁺), 563.8 (25%, M+Na⁺).

- 30 MS FAB: For C₂₅H₃₃O₅N₇P, requires 542.228081, found 542.228131.

HPLC: t_R 31.76, 32.03 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3334.1 (N-Hstr.), 1734.5 (C=Ostr.), 1595.9, 1488.0 (aromatic C-Cstr.), 1450.3 (C-Hdef.), 1394.2 (-CH₃sym.def.), 1252.8 (P=O), 1210.4 (P-O-aryl), 1153.3 (C-Ostr.), 1026.0 (P-O-alkyl), 934.8 (olefinic C-Hdef.), 759.0 (monosub.aromatic C-Hdef.).

5 Phenyl-(benzoxy-L-alaninyl)-phosphorochloridate.



This was synthesised according to Standard Procedure 3, using L-alanine benzyl ester hydrochloride (1.0g, 4.64mmol), PhOP(O)Cl₂ (0.98g, 0.69ml, 4.64mmol) and NEt₃ (0.94g, 1.29ml, 9.27mmol) to yield 1.61g (98.2%) of crude product that was stored in anhydrous THF (10ml), to give a 0.46mmol/ml solution that was used without further purification.

³¹P NMR: δ 9.41, 9.23 (1:1).

¹H NMR: δ 7.41-7.21 (10H,m,2xPh); 5.24 (2H,d,CH₂Ph), 4.95-4.88 (1H,t,NHala), 4.36-4.15 (1H,m,CHala), 1.56 (3H,t,CH₃ala).

¹³C NMR: δ 172.9 (CO), 150.2 ('*ipso*'-OPh), 135.5 ('*ipso*'-CH₂Ph), 130.3 ('*m'*-OPh), 129.0 ('*o'*-CH₂Ph), 128.7 ('*m'*+'*p*'-CH₂Ph), 126.4 ('*p*'-OPh), 121.0 ('*o*'-OPh), 68.0 (OCH₂), 51.1 (CHala), 20.8 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-[phenyl-(benzoxy-L-alaninyl)]-phosphate. Cf1582.



This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (400mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (2.1ml, 2.1mmol), and phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (0.46M solution in THF) (9.2ml, 4.19mmol) in anhydrous THF (20ml), and stirring at room temperature for 64hrs. The crude product was purified by column chromatography eluting with 3% MeOH in CHCl₃, and then 2.5% MeOH in CHCl₃ to give the product as a white foam (82.2mg, 9.75%).

A second synthesis was undertaken with (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (200mg, 0.7mmol), tBuMgCl (2.43ml of a 1.0M soln in THF, 2.43mmol), and phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (2.2ml of a 0.46M soln in THF, 2.1mmol) in THF (2.5ml). Purification by column chromatography eluting with 3% MeOH in CHCl₃ gave the pure product as a white foamy solid (90mg, 21.3%).

³¹P NMR: δ 3.82, 3.72 (1:1).

¹H NMR: δ 7.51 (1H,d,H8), 7.37-7.15 (10H,m,OPh+CH₂Ph), 6.10-6.04 (1H,m,H2'), 5.96 (1H,bs,NHcPr), 5.89 (1H,dd,J=5.36Hz,H3'), 5.54 (1H,t,H1'), 5.16 (2H,bs,NH₂), 4.96 (2H,bs,CH₂Ph), 4.23-4.05 (3H,m,NHala+H5'), 3.89-3.70 (1H,dt,CHala), 3.16-3.12 (1H,t,H4'), 3.03 (1H,bs,CHcPr), 2.85-2.71 (1H,m,1of H6'), 1.74-1.64 (1H,m,1of H6'), 1.44-1.39 (3H,t,J=7.84Hz,CH₃ala), 0.88 (2H,q,J=6.75Hz,2H of CH₂cPr), 0.64 (2H,m,2H of CH₂cPr).

¹³C NMR: δ 173.3 (CO), 159.7 (C2), 156.0 (C4), 150.9 (C6), 150.7 ('ipso'-OPh), 136.4 (C2'), 135.7 ('ipso'-Bn), 135.2 (C8), 131.0 (C3'), 129.6 ('o'-Bn), 128.6 ('m'-Bn), 128.5 (p'-Bn), 128.2 ('m'-OPh), 124.9 ('p'-OPh), 120.1 ('o'-OPh), 114.8 (C5), 68.8 (C5'), 67.2 (CH₂Ph), 58.9 (C1'), 50.3 (CHala), 45.6 (C4'), 34.4 (C6'), 23.7 (CHcPr), 21.0 (CH₃ala), 7.4 (CH₂cPr).

MS ES⁺ : m/z 603.8 (100%, M⁺), 604.8 (30%, M+H⁺), 625.7 (20%, M+Na⁺).

MS FAB: For C₃₀H₃₅O₅N₇P requires 604.243731, found 604.241775.

15 HPLC: t_R 33.39 (99.7%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3355.9 (N-Hstr.), 2923.3, 2853.7 (C-Hstr.), 1734.1 (C=Ostr.), 1595.6 (aromatic C-Cstr.), 1458.4 (C-Hdef.), 1376.5 (-CH₃sym.def.), 1154.4 (C-Ostr.), 1028.2 (P-O-alkyl), 935.8 (olefinic C-Hdef.), 721.7 (monosub.aromatic C-Hdef.).

20

L-Alanine n-propyl ester hydrochloride salt.

C₆H₁₄N₁O₂Cl₁, MW=167.634

This was synthesised according to Standard Procedure 1, using anhydrous propan-1-ol (42.0ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The 25 product was isolated as a white solid (8.88g, 94.3%).

¹H NMR (MeOH-d₄): δ 4.34-4.26 (2H,m,OCH₂), 4.24-4.17 (1H,q,CHala), 1.88-1.78 (2H,m,CH₂), 1.65 (3H,d,J=7.24Hz,CH₃ala), 1.10-1.05 (3H,t,CH₂CH₃).

¹³C NMR: δ 170.1 (CO), 68.0 (OCH₂), 48.9 (CHala), 21.9 (CH₂), 15.3 (CH₃ala), 9.5 (CH₂CH₃).

30

Phenyl-(n-propoxy-L-alaninyl)-phosphorochloridate

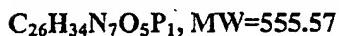
C₁₂H₁₇N₁O₄P₁Cl₁, MW=305.79

This was synthesised according to **Standard Procedure 3**, using L-Alanine *n*-propyl ester hydrochloride salt (0.5g, 2.98mmol), PhOP(O)Cl₂ (0.45ml, 2.98mmol), triethylamine (0.83ml, 5.97mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (0.84g, 92.1%), which was stored in THF (5ml) to give a 0.55M solution.

- 5 ³¹P NMR: δ 9.41, 9.17 (1:1).
- 10 ¹³C NMR: δ 173.1 (CO), 150.1 ('*ipso*'-Ph), 130.0 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 67.9 (OCH₂), 51.0 (CHala), 22.3 (CH₂CH₃), 21.0 (CH₃ala), 10.7 (CH₂CH₃).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

10 **O-Phenyl-(*n*-propoxy-L-alaninyl)-phosphate. Cf1646.**



This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-propyl-L-alaninyl)-phosphorochloridate (1.9ml, 1.05mmol, of a 0.55M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ to give the pure product as a pale yellow foamy solid (123mg, 63.4%).

- 5 ³¹P NMR: δ 4.06, 3.98 (1:1).
- 10 ¹H NMR: δ 7.40 (1H,d,J=7.99Hz,H8), 7.23-7.18 (2H,dd,'*o*'-Ph), 7.12-7.02 (3H,m,'*m*'+'*p*'-Ph), 6.16 (1H,bs,H3'), 5.96 (1H,t,H2'), 5.78 (1H,d,J=5.83Hz,NHcycl), 5.44 (1H,bs,H1'), 5.15 (2H,bs,NH₂), 4.33-4.18 (1H,m,CHala), 4.15-4.04 (2H,m,OCH₂), 4.01-3.88 (2H,m,H5'), 3.65 (1H,bs,NHala), 3.03 (1H,d,H4'), 2.92 (1H,bs,CHcycl), 2.72-2.62 (1H,m,1of H6'), 1.60-1.47 (3H,m,1of H6'+CH₂CH₃), 1.30-1.26 (3H,t,CH₃ala), 0.84-0.80 (3H,m,CH₂CH₃), 0.73 (2H,d,J=6.8Hz,1of CH₂cycl), 0.51 (2H,bs,1of CH₂cycl).
- 15 ¹³C NMR: δ 174.1CO 160.4 (C2), 156.6 (C4), 151.1 (C6+'*ipso*'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 67.4 (OCH₂), 59.2 (C1'), 50.6 (CHala), 46.0 (C4'), 35.0 (C6'), 24.2 (CHcPr), 22.3 (CH₂CH₃), 21.5 (CH₃ala), 10.7 (CH₂CH₃), 7.7 (CH₂cycl).
- 20 MS ES⁺: m/z 555.8 (100%, M⁺), 557.0 (30%, M+H⁺).
- 25 MS FAB: For C₂₆H₃₅O₅N₇P requires 556.2437, found 556.2438.
- 30 HPLC: t_R 34.708 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *n*-butyl ester hydrochloride salt.**C₇H₁₆N₁O₂Cl₁, MW=181.661**

This was synthesised according to Standard Procedure 1, using anhydrous butan-1-ol (51.4ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (8.86g, 86.9%).

¹H NMR (MeOH-d₄): δ 4.29-4.17 (2H,m,OCH₂), 4.13-4.06 (1H,q,CHala), 1.71-1.62 (2H,m,OCH₂CH₂), 1.53 (3H,d,J=7.25Hz,CH₃ala), 1.47-1.34 (2H,m,CH₂CH₃), 0.96-0.91 (3H,t,CH₂CH₃).

¹³C NMR: δ 170.1 (CO), 66.2 (OCH₂), 48.9 (CHala), 30.6 (OCH₂CH₂), 19.0 (CH₂CH₃), 15.3 (CH₃ala), 13.0 (CH₂CH₃).

Phenyl-(*n*-butoxy-L-alaninyl)-phosphorochloridate**C₁₃H₁₉N₁O₄P₁Cl₁, MW=317.82**

This was synthesised according to Standard Procedure 3, using L-Alanine *n*-butyl ester hydrochloride salt (0.5g, 2.75mmol), PhOP(O)Cl₂ (0.41ml, 2.75mmol), triethylamine (0.77ml, 5.5mmol) in DCM (80ml). The usual workup yielded the crude product as a yellow oil (0.84g, 94.5%), which was stored in THF (5ml) to give a 0.525M solution.

³¹P NMR: δ 9.39, 9.10 (1:1).

¹H NMR: δ 7.43-7.15 (5H,m,Ph), 4.68-4.59 (1H,q,CHala), 4.27-4.05 (3H,m,OCH₂+NHala), 1.73-1.59 (2H,m,OCH₂CH₂), 1.56-1.53 (2H,dd,CH₂CH₃), 1.46-1.37 (3H,m,CH₃ala), 1.00-0.92 (3H,m,CH₂CH₃).

¹³C NMR: δ 173.2 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 66.2 (OCH₂), 51.0 (CHala), 30.9 (OCH₂CH₂), 21.0 (CH₃ala), 19.4 (CH₂CH₃), 14.1 (CH₂CH₃).

25

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-Phenyl-(*n*-butoxy-L-alaninyl)-phosphate. Cf1647.****C₂₇H₃₆N₇O₅P₁, MW=569.597**

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-butyl-L-alaninyl)-phosphorochloridate (2.0ml, 1.05mmol, of a 0.525M solution in THF), at room

temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ to give the pure product as a pale yellow foamy solid (157mg, 78.9%).

³¹P NMR: δ 4.01, 3.95 (1:1).

- ¹H NMR: δ 7.40 (1H,d,J=7.32Hz,H8), 7.23-7.18 (2H,t,'o'-Ph), 7.11 (2H,t,'m'-Ph), 7.04 (1H,t,'p'-Ph), 6.02 (1H,bs,H3'), 5.97 (1H,t,H2'), 5.78 (1H,bs,NHcycl), 5.44 (1H,bs,H1'), 5.06 (2H,bs,NH₂), 4.22-3.88 (6H,m,CHala,OCH₂,H5'+NHala), 3.05 (1H,d,H4'), 2.93 (1H,bs,CHcycl), 2.72-2.62 (1H,m,1of H6'), 1.61-1.47 (3H,m,1of H6'+OCH₂CH₂), 1.30-1.26 (5H,t,CH₃ala+CH₂CH₃), 0.85-0.80 (3H,t,CH₂CH₃), 0.74 (2H,d,J=6.45Hz,1of CH₂cycl), 0.51 (2H,bs,1of CH₂cycl).
- 10 ¹³C NMR: δ 174.1(CO), 160.4 (C2), 156.7 (C4), 151.2 (C6), 151.1 ('ipso'-Ph), 136.7 (C2'), 135.8 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.5 ('o'-Ph), 115.0 (C5), 69.3 (C5'), 65.8 (OCH₂), 59.2 (C1'), 50.6 (CHala), 46.0 (C4'), 35.0 (C6'), 30.9 (OCH₂CH₂), 24.1 (CHcPr), 21.5 (CH₃ala), 19.4 (CH₂CH₃), 14.1 (CH₂CH₃), 7.8 (CH₂cycl).
- MS ES⁺: m/z 569.9 (70%, M⁺), 570.9 (20%, M+H⁺), 591.8 (100%, M+Na⁺), 607.8 (20%, M+K⁺).

HPLC: t_R 38.27 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine i-propyl ester hydrochloride salt.

20 C₆H₁₄N₁O₂Cl₁, MW=167.634

This was synthesised according to Standard Procedure 1, using anhydrous propan-2-ol (43.0ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a semicrystalline solid (8.86g, 86.9%).

- ¹H NMR (MeOH-d₄): δ 5.16-5.08 (1H,m,CHala), 4.11-4.04 (1H,q,OCH(Me)₂), 1.55 (3H,d,J=7.21Hz,CH₃ala), 1.34-1.31 (6H,dd,CH(Me)₂).
- ¹³C NMR: δ 169.5 (CO), 70.8 (COCH(Me)₂), 48.9 (CHala), 20.8 (CH₃ala), 15.3 (CH(Me)₂).

Phenyl-(i-propoxy-L-alaninyl)-phosphorochloridate

30 C₁₂H₁₇N₁O₄P₁Cl₁, MW=305.79

This was synthesised according to Standard Procedure 3, using L-Alanine i-propyl ester hydrochloride salt (0.5g, 2.98mmol), PhOP(O)Cl₂ (0.45ml, 2.98mmol), triethylamine

(0.83ml, 5.97mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.12g, >100%), which was stored in THF (5ml) to give a 0.597M solution.

³¹P NMR: δ 9.45, 9.17 (1:1).

¹³C NMR: δ 172.6 (CO), 150.2 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph),

5 70.1 (OCH), 51.1 (CHala), 22.1 (CH(CH₃)₂), 20.9 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-Phenyl-(*i*-propoxy-L-alaninyl)-phosphate. Cf1661.

C₂₆H₃₄N₇O₅P₁, MW=555.57

- 10 This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*i*-propyl-L-alaninyl)-phosphorochloride (1.76ml, 1.05mmol, of a 0.597M solution in THF), at room temperature for 72hrs. The crude product was purified by eluting with 3% MeOH
- 15 in CHCl₃ (x2) to give the pure product as a pale yellow foamy solid (106.8mg, 54.8%).

³¹P NMR: δ 4.02, 3.98 (1:1).

¹H NMR: δ 7.41 (1H,d,J=8.12Hz,H8), 7.24-7.19 (2H,m,'*o*'-Ph), 7.13-7.03 (3H,m,'*m*'+'*p*'-Ph), 6.37 (1H,bs,,NHcPr), 5.98 (1H,t,H3'), 5.80-5.76 (1H,m,H2'), 5.43 (1H,bs,H1'), 5.21 (2H,bs,NH₂), 4.94-4.86 (1H,m,OCH), 4.15-3.98 (2H,m,H5'), 3.92-3.83 (1H,m,CHala),

20 3.59 (1H,bs,NHala), 3.06-2.98 (1H,m,H4'), 2.93 (1H,bs,CHcPr), 2.74-2.63 (1H,m,1of H6'), 1.62-1.53 (1H,m,1of H6'), 1.34-1.18 (3H,m,CH₃ala), 1.15-1.11 (6H,m,CH(CH₃)₂), 0.79-0.73 (2H,q,2Hof CH₂cPr), 0.53 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 173.5(CO) 159.8 (C2), 156.2 (C4), 151.1 (C6), 151.0 ('*ipso*'-Ph), 136.9 (C2'), 136.1 (C8), 131.3 (C3'), 130.0 ('*m*'-Ph), 125.3 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.6

25 (C5'), 69.2 (OCH), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 22.0 (CH(CH₃)₂), 21.4 (CH₃ala), 7.8 (CH₂cycl).

□S ES⁺: m/z 555.9 (100%, M⁺), 556.9 (30%, M+H⁺).

MS MALDI TOF: For C₂₆H₃₅O₅N₇P found 555.575.

HPLC: t_R 35.85 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins),

30 100% water (55mins)).

Phenyl-*tert*butyloxy-L-alaninyl phosphorochloride.

C₁₆H₁₇O₄N₁Cl₁P₁, MW=353.74.

This was synthesised according to **Standard Procedure 3**, using L-alanine *tert*-butyl ester hydrochloride (0.5g, 2.75mmol), PhOP(O)Cl₂ (0.41ml, 2.75mmol) and NEt₃ (0.77ml, 5.5mmol) to yield 0.77g (87.5%) of crude product that was stored in anhydrous THF (5ml), to give a 0.48mmol/ml solution that was used without further purification.

5 ³¹P NMR: δ 9.53, 9.20 (1:1).

¹H NMR: δ 7.44-7.39 (2H,t,'o'-Ph), 7.32-7.26 (3H,m,'m'+'p'-Ph), 4.47-4.34 (1H,m,NHala), 4.17-4.04 (1H,m,CHala), 1.53 (9H,3s,3xCH₃).

¹³C NMR: δ 170.7 (CO), 148.7 ('ipso'-Ph), 128.9 ('o'-Ph), 124.9 ('p'-Ph), 119.5 ('m'-Ph), 81.65 (CMe₃), 50.0 (CHala), 26.9 (3xCH₃).

10

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl-*tert*butoxy-L-alaninyl)-phosphate. Cf1645.

C₂₄H₃₀O₅N₇P₁, MW=603.6.

This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (140mg, 0.52mmol), tBuMgCl (1.05ml, 1.05mmol of a 1.0M solution in THF), and phenyl-(*tert*butoxy-L-alaninyl)-phosphorochloridate (3.3ml, 1.57mmol, of a 0.48M solution in THF), in anhydrous THF (4ml) stirring at room temperature for 48hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ to give the pure product as white foamy solid 20 (192.3mg, 69.0%).

³¹P NMR: δ 4.15 (s).

¹H NMR: δ 7.40 (1H,d,J=8.35Hz,H8), 7.23-7.18 (2H,t,'m'-Ph), 7.12 (2H,d,'o'-Ph), 7.06-7.02 (1H,t,'p'-Ph), 6.09 (1H,bs,H2'), 5.97 (1H,bs,H3'), 5.77 (1H,d,NHcPr), 5.44 (1H,bs,H1'), 5.10 (2H,bs,NH₂), 4.14-4.05 (3H,m,H5'+NHala), 3.85-3.77 (1H,d,CHala), 25 3.04 (1H,bs,H4'), 2.93 (1H,bs,CHcPr), 2.72-2.62 (1H,m,1of H6'), 1.58-1.53 (1H,t,1of H6'), 1.34 (9H,d,CMe₃), 1.27-1.23 (3H,t,CH₃ala), 0.73 (2H,d,2Hof CH₂cPr), 0.51 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 173.2 (CO), 160.4 (C2), 156.7 (C4), 151.2 (C6+'ipso'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.6 ('o'-Ph), 115.2 (C5), 82.3 (C[CH₃]₃), 69.3 (C5'), 59.1 (C1'), 46.0 (C4'), 35.0 (C6'), 28.3 (3xCH₃), 24.2 (CHcPr), 21.5 (CH₃ala), 7.8 (CH₂cPr).

MS ES⁺: m/z 570.0 (100%, M⁺), 570.9 (32%, M+H⁺).

MS FAB: For C₂₇H₃₇O₅N₇P requires 570.2594, found 570.2598.

HPLC: t_R 36.158 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *n*-pentyl ester hydrochloride salt

5 C₈H₁₆N₁O₂Cl₁, MW=195.69

This was synthesised according to **Standard Procedure 1**, using pentan-1-ol (36.3ml, 0.337mol), thionyl chloride (4.92ml, 67.4mmol) and L-Alanine (3.0g, 33.7mmol). The product was isolated as a white solid pure product (4.86g, 73.7%).

¹H NMR (MeOH-d₄): δ 4.32-4.20 (2H,m,OCH₂), 4.16-4.08 (1H,m,CHala), 1.77-1.68 (2H,m,OCH₂CH₂), 1.56 (3H,d,J=7.22Hz,CH₃ala), 1.42-1.36 (4H,m,CH₂CH₂CH₃), 0.97-0.93 (3H,m,CH₂CH₃).

¹³C NMR: δ 170.1 (CO), 66.5 (OCH₂), 48.8 (CHala), 28.2 (OCH₂CH₂), 28.0 (CH₂CH₂CH₃), 22.3 (CH₂CH₃), 15.2 (CH₃ala), 13.3 (CH₂CH₃).

15 Phenyl-(*n*-pentoxy-L-alaninyl)-phosphorochloridate

C₁₄H₂₁N₁O₄P₁Cl₁, MW=333.78

This was synthesised according to **Standard Procedure 3**, using L-Alanine *n*-pentyl ester hydrochloride salt (0.5g, 2.56mmol), PhOP(O)Cl₂ (0.38ml, 2.56mmol), triethylamine (0.71ml, 5.11mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (0.79g, 92.6%), which was stored in THF (5ml) to give a 0.47M solution.

³¹P NMR: δ 9.39, 9.12 (1:1).

¹H NMR: δ 7.43-7.38 (2H,m,'o'-Ph), 7.32-7.25 (3H,m,'m'+'p'-Ph), 4.63 (1H,bd,NHala), 4.24-4.11 (3H,m,OCH₂+CHala), 1.73-1.65 (2H,m,OCH₂CH₂), 1.57-1.53 (3H,dd,CH₃ala), 1.42-1.35 (4H,m,2xCH₂), 0.97-0.91 (3H,m,CH₂CH₃).

¹³C NMR: δ 173.1 (CO), 150.1 ('ipso'-Ph), 130.3 ('m'-Ph), 126.4 ('p'-Ph), 121.0 ('o'-Ph), 66.5 (OCH₂), 51.0 (CHala), 28.6 (CH₂-C2), 28.3 (CH₂-C3), 22.7 (CH₂-C4), 21.0 (CH₃ala), 14.1 (CH₃-C5).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

30 O-Phenyl-(*n*-pentyloxy-L-alaninyl)-phosphate. Cf1706.

C₂₈H₃₈N₇O₅P₁, MW=583.7

This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol),

tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-pentyl-L-alaninyl)-phosphorochloridate (2.22ml, 1.05mmol, of a 0.47M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 2.5-3.0% MeOH in CHCl₃, (x2) to give the pure product as a pale yellow foamy solid (143.2mg, 5 70.2%).

³¹P NMR: δ 3.99, 3.95 (1:1).

¹H NMR: δ 7.41 (1H,d,J=7.18Hz,H8), 7.24-7.19 (2H,m,'o'-Ph), 7.12-7.02 (3H,m,'m'+*p*'-Ph), 6.09 (1H,bs,NHcPr), 5.98 (1H,d,H2'), 5.79 (1H,bs,H3'), 5.44 (1H,bs,H1'), 5.09 (2H,bs,NH₂), 4.16-3.88 (6H,m,CHala,OCH₂,H5'+NHala), 3.05 (1H,bs,H4'), 2.94 (1H,bs,CHcPr), 2.73-2.63 (1H,m,1of H6'), 1.62-1.51 (3H,m,1of H6'+OCH₂CH₂), 1.31-1.21 (7H,t,CH₃ala+2xCH₂), 0.81-0.74 (5H,m,CH₃+2Hof CH₂cPr), 0.52 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 174.1(CO), 160.1 (C2), 156.5 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.8 (C2'), 136.1 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.1 (C5), 69.3 (C5'), 66.1 (OCH₂), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 28.6 (CH₂-C2), 28.3 (CH₂-C3), 24.2 (CHcPr), 22.6 (CH₂-C4), 21.5 (CH₃ala), 14.3 (CH₃-C5), 7.8 (CH₂cPr).

MS ES⁺: m/z 584.2 (100%, M⁺), 585.2 (25%, M+H⁺).

MS FAB: For C₂₈H₃₉O₅N₇P requires 584.2750, found 584.2757.

HPLC: t_R 40.294 (99.3%)-(100% water (0mins), 20% water (35mins), 20% water 20 (45mins), 100% water (55mins)).

L-Alanine *n*-hexyl ester hydrochloride salt

C₉H₂₀N₁O₂Cl₁, MW=209.75

This was synthesised according to Standard Procedure 2, using L-Alanine (2.0g, 25 22.5mmol), hexan-1-ol (2.82ml, 22.5mmol), *p*-toluene sulfonic acid monohydrate (4.7g, 24.7mmol), and toluene (100ml). L-alanine *n*-hexyl ester hydrochloride was isolated as a white powdery solid (3.32g, 70.5%).

¹H NMR (MeOH-d₄): δ 4.31-4.18 (2H,m,OCH₂), 4.17-4.09 (1H,q,CHala), 1.75-1.66 (2H,m,OCH₂CH₂), 1.57 (3H,d,J=7.20Hz,CH₃ala), 1.45-1.35 (6H,m,[CH₂]₃CH₃), 0.94-0.89 (3H,t,CH₂CH₃).

¹³C NMR: δ 170.1 (CO), 66.5 (OCH₂), 48.9 (CHala), 31.6 (OCH₂CH₂), 28.6 (O[CH₂]₂CH₂), 25.6 (CH₂CH₂CH₃), 22.6 (CH₂CH₃), 15.4 (CH₃ala), 13.4 (CH₂CH₃).

Phenyl-(n-hexyloxy-L-alaninyl)-phosphorochloridate**C₁₅H₂₃N₁O₄P₁Cl₁, MW=347.81**

This was synthesised according to Standard Procedure 3, using L-Alanine *n*-hexyl ester hydrochloride salt (0.5g, 2.38mmol), PhOP(O)Cl₂ (0.36ml, 2.38mmol), triethylamine 5 (0.66ml, 4.77mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (0.69g, 83.2%), which was stored in THF (4ml) to give a 0.496M solution.

³¹P NMR: δ 9.40, 9.10 (1:1).

¹H NMR: δ 7.44-7.14 (5H,m,OPh), 4.25 (1H,bs,NHala), 4.23-4.03 (3H,m,OCH₂+CHala), 1.70-1.63 (2H,m,CH₂-2), 1.57-1.54 (2H,m,CH₂-3), 1.47-1.32 (7H,m,CH₃ala+2CH₂-4,5), 10 0.93-0.91 (3H,dd,CH₃-6).

¹³C NMR: δ 173.2 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 120.9 ('*o*'-Ph), 66.4 (OCH₂), 51.0 (CHala), 31.7 (CH₂-C2), 28.9 (CH₂-C3), 25.8 (CH₂-C4), 22.9 (CH₂-C5), 21.0 (CH₃ala), 14.4 (CH₃-C6).

15 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-Phenyl-(n-hexyloxy-L-alaninyl)-phosphate.

C₂₉H₄₀N₇O₅P₁, MW=597.651

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-hexyloxy-L-alaninyl)-phosphorochloridate (2.11ml, 1.05mmol, of a 0.496M solution in THF), at room temperature for 24hrs. Additional phenyl-(*n*-hexyloxy-L-alaninyl)-phosphorochloridate (1.5ml, 0.68mmol, of a 0.496M solution in THF), was added and the reaction stirred for a further 24hrs. The crude product was purified by eluting with 3.0% MeOH in CHCl₃ (x2) to give the pure product as a pale yellow foamy solid.

³¹P NMR: δ 3.94, 3.91 (1:1).

¹H NMR: δ 7.52 (1H,d,J=8.00Hz,H8), 7.36-7.31 (2H,m,'*o*'-Ph), 7.25-7.15 (3H,m,'*m*'+'*p*'-Ph), 6.26 (1H,bs,NHcPr), 6.13-6.08 (1H,m,H2'), 5.93-5.88 (1H,m,H3'), 5.58-5.53 (1H,m,H1'), 5.14 (2H,bs,NH₂), 4.28-3.89 (6H,m,CHala,OCH₂,H5'+NHala), 3.17 (1H,t,H4'), 3.04 (1H,bs,CHcPr), 2.87-2.75 (1H,m,1of H6'), 1.74-1.61 (3H,m,1of H6'+OCH₂CH₂), 1.43-1.31 (9H,t,CH₃ala+3xCH₂), 0.92-0.85 (5H,m,CH₃+2Hof CH₂cPr), 0.68-0.63 (2H,q,2Hof CH₂cPr).

¹³C NMR: δ 174.1(CO), 160.1 (C2), 156.5 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.9 (C2'), 136.0 (C8), 131.4 (C3'), 130.0 ('*m*'-Ph), 125.3 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 66.1 (OCH₂), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 31.7 (OCH₂CH₂), 28.8 (CH₂-ester), 25.8 (CH₂-ester), 24.2 (CHcPr), 21.9 (CH₂-ester), 21.5 (CH₃ala), 14.4 5 (CH₃-ester), 7.8 (CH₂cPr).

L-Alanine cyclo-hexyl ester hydrochloride salt

C₉H₁₆N₁O₂Cl₁, MW=205.71

This was synthesised according to Standard Procedure 2, using L-Alanine (2.0g, 10 22.5mmol), cyclohexanol (2.34ml, 22.5mmol), *p*-toluene sulfonic acid monohydrate (4.7g, 24.7mmol), and toluene (100ml). The *p*-toluene sulfonate salt was isolated as a pale orange solid (1.45g).

The reaction was repeated using L-Alanine (3.0g, 33.7mmol), cyclohexanol (5.26ml, 15 50.6mmol), *p*-toluene sulfonic acid monohydrate (9.62g, 50.6mmol), and toluene (100ml). L-alanine cyclohexyl ester hydrochloride salt was isolated as a white solid (3.15g, 45.45%).

¹H NMR (MeOH-d₄): δ 4.90 (1H,m,OCH), 4.12-4.04 (1H,q,CHala), 1.92-1.81 (2H,m,OCHCH₂), 1.80-1.63 (2H,m,OCHCH₂), 1.55 (3H,d,J=7.23Hz,CH₃ala), 1.49-1.33 20 (6H,m,[CH₂]₃).

¹³C NMR: δ 169.5 (CO), 75.4 (OCH), 48.9 (CHala), 31.3 (2xCH₂-*o*), 25.2 (2xCH₂-*m*), 23.5 (*p*-CH₂), 15.3 (CH₃ala).

Phenyl-(*c*-hexyloxy-L-alaninyl)-phosphorochloridate

25 C₁₅H₂₁N₁O₄P₁Cl₁, MW=345.79

This was synthesised according to Standard Procedure 3, using L-Alanine *c*-hexyl ester hydrochloride salt (0.7g, 3.4mmol), PhOP(O)Cl₂ (0.51ml, 3.4mmol), triethylamine (0.95ml, 6.8mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (1.12g, 95.2%), which was stored in THF (7ml) to give a 0.46M solution.

30 ³¹P NMR: δ 9.43, 9.07 (1:1).

¹H NMR: δ 7.44-7.33(2H,m,'*o*'-Ph), 7.32-7.20 (3H,m,'*m*'+'*p*'-Ph), 4.92-4.83 (1H,m,OCH), 4.55-4.42 (1H,m,NHala), 4.28-4.15 (1H,m,CHala), 1.89 (2H,bd,CH₂-'*o*'), 1.76 (1H,bd,CH₂-'*o*'), 1.54 (3H,d,CH₃ala), 1.49-1.32 (6H,m,CH₃3CH₂-'*m*'+'*p*').

¹³C NMR: δ 172.5 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 74.9 (OCH), 51.1 (CHala), 31.8 (CH₂-'*o*'), 25.6 (CH₂-'*p*'), 21.0 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

5 **O-Phenyl-(c-hexyloxy-L-alaninyl)-phosphate. C₁₁H₂₀N₇O₅P₁.**

C₂₉H₃₈N₇O₅P₁, MW=595.635

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(c-hexoxy-L-alaninyl)-phosphorochloridate (2.28ml, 1.05mmol, of a 0.46M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3-4% MeOH in CHCl₃, and then 2.5-3.0% MeOH in CHCl₃ to give the pure product as a pale yellow foamy solid (199mg, 95.7%).

³¹P NMR: δ 4.06, 3.99 (1:1).

15 ¹H NMR: δ 7.42 (1H,d,J=8.15Hz,H8), 7.23-7.18 (2H,m,'*o*'-Ph), 7.12-7.02 (3H,m,'*m*'+'*p*'-Ph), 6.31 (1H,bs,NHcPr), 5.98 (1H,bs,H2'), 5.78 (1H,bs,H3'), 5.43 (1H,bs,H1'), 5.21 (2H,bs,NH₂), 4.66 (1H,bs,OCH), 4.17-4.02 (3H,m,H5'+NHala), 3.95-3.85 (1H,m,CHala), 3.05-2.94 (2H,m,H4'+CHcPr), 2.73-2.63 (1H,m,1of H6'), 1.69 (2H,bs,CH₂-'*o*'), 1.62-1.53 (2H,m,CH₂-'*m*'), 1.45-1.18 (9H,m,CH₃ala+3xCH₂-'*m*'+'*p*'), 0.76 (2H,d,2Hof CH₂cPr), 20 0.53 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 172.0CO, 158.4 (C2), 154.8 (C4), 149.7 (C6), 149.6 ('*ipso*'-Ph), 135.5 (C2'), 134.7 (C8), 130.0 (C3'), 128.6 ('*m*'-Ph), 123.8 ('*p*'-Ph), 119.1 ('*o*'-Ph), 113.1 (C5), 72.9 (OCH), 67.8 (C5'), 57.9 (C1'), 59.4 (CHala), 44.7 (C4'), 34.5 (C6'), 30.3 (CH₂-'*o*'), 24.2 (CH₂-'*m*'), 22.8 (CHcPr), 22.5 (CH₂-'*p*'), 20.1 (CH₃ala), 6.4 (CH₂cPr).

25 MS ES⁺: m/z 596.2 (100%, M⁺), 597.3 (20%, M+H⁺).

MS FAB: For C₂₉H₃₉O₅N₇P requires 596.2750, found 596.2750.

HPLC: t_R 40.502 (99.8%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

30 **L-alanine cyclohexane-methyl ester hydrochloride**

C₁₀H₂₀N₁O₂Cl₁, MW=221.75

This was synthesised according to Standard Procedure 2, using L-Alanine (3.0g, 33.7mmol), cyclohexane methanol (4.15ml, 33.7mmol), *p*-toluene sulfonic acid

monohydrate (7.05g, 37.1mmol), and toluene (100ml). 9.2g of the the PTSA salt was solubilised in DCM (50ml), and washed with 10% K₂CO₃ (50ml), and water (2x50ml), dried over MgSO₄, filtered and the filtrate reduced to dryness to give a yellow oil. This was neutralised with 2M HCl, stirred for 2hrs, and then freeze-dried to give the hydrochloride salt as a white solid (4.32g, 75.8%).

¹H NMR (MeOH-d₄): δ 4.19-4.01 (3H,m,OCH+CHala), 1.79-1.69 (5H,m,CH+o-CH₂), 1.58 (3H,d,J=7.21Hz,CH₃ala), 1.37-1.20 (4H,m,m-CH₂), 1.09-0.98 (2H,q,p-CH₂).

¹³C NMR: δ 170.1 (CO), 71.3 (OCH₂), 48.9 (CHala), 37.3 (CH), 29.5 (2xCH₂-o), 26.4 (p-CH₂), 25.7 (2xCH₂-m), 15.4 (CH₃ala).

10

Phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphorochloridate

C₁₆H₂₃N₁O₄P₁Cl₁, MW=359.82

This was synthesised according to **Standard Procedure 3**, using L-Alanine cyclohexane-methyl ester hydrochloride salt (0.7g, 3.16mmol), PhOP(O)Cl₂ (0.47ml, 3.16mmol), triethylamine (0.88ml, 6.31mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.10g, 96.8%), which was stored in THF (6ml) to give a 0.51M solution.

³¹P NMR: δ 9.35, 9.05 (1:1).

¹H NMR: δ 4.61-4.50 (1H,q,NHala), 4.28-4.13 (1H,m,CHala), 4.04-4.00 (2H,q,OCH₂), 1.78-1.74 (7H,t,CHcHx+'o'-CH₂), 1.57-1.54 (3H,dd,CH₃ala), 1.06-0.96 (2H,q,'p'-CH₂).

¹³C NMR: δ 173.1 (CO), 150.1 ('ipso'-Ph), 130.3 ('m'-Ph), 126.4 ('p'-Ph), 121.0 ('o'-Ph), 71.4 (OCH₂), 51.0 (CHala), 37.4 (CHcHx), 29.9 (CH₂-'o'), 26.7 (CH₂-'m'), 25.9 (CH₂-'p'), 21.1 (CH₃ala).

25 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-Phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphate. Cf1708.

C₃₀H₄₀N₇O₅P₁, MW=609.66

This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphorochloridate (2.06ml, 1.05mmol, of a 0.51M solution in THF), at room temperature for 48hrs. The crude product was purified by eluting

with 4-6% MeOH in DCM, and then 3% MeOH in CHCl₃ to give the pure product as a pale yellow foamy solid (161.1mg, 75.6%).

³¹P NMR: δ 3.99, 3.92 (1:1).

- ¹H NMR: δ 7.40 (1H,d,J=7.07Hz,H8), 7.24-7.19 (2H,t,'o'-Ph), 7.13-7.03 (3H,m,'m'+'p'-Ph), 6.00-5.96 (2H,m,H2'+NHcPr), 5.79 (1H,q,H3'), 5.45 (1H,d,H1'), 5.05 (2H,bs,NH₂), 4.16-4.01 (3H,m,OCH₂+NHala), 3.98-3.88 (1H,m,CHala), 3.86-3.74 (2H,m,HS'), 3.07-3.00 (1H,t,H4'), 2.94 (1H,bs,CHcPr), 2.74-2.63 (1H,m,1of H6'), 1.88-1.50 (7H,m,CHcHx+2CH₂-'o'), 1.31-1.27 (3H,t,CH₃ala), 1.21-0.99 (4H,m,2CH₂-'m'), 0.89-0.79 (2H,q,CH₂-'p'), 0.75 (2H,d,2Hof CH₂cPr), 0.54-0.50 (2H,t,2Hof CH₂cPr).
- 10 ¹³C NMR: δ 174.1(CO), 160.2 (C2), 156.4 (C4), 151.2 (C6), 151.1 ('ipso'-Ph), 136.7 (C2'), 136.0 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.5 ('o'-Ph), 115.1 (C5), 71.0 (OCH₂), 69.3 (C5'), 59.3 (C1'), 50.7 (CHala), 46.1 (C4'), 37.4 (CHcHx), 34.9 (C6'), 29.9 (CH₂-'o'), 26.6 (CH₂-'m'), 25.9 (CH₂-'p'), 24.2 (CHcPr), 21.5 (CH₃ala), 7.8 (CH₂cPr).
MS ES⁺: m/z 610.3 (50%, M+H⁺), 632.3 (100%, M+Na⁺), 633.3 (M+H+Na⁺).
- 15 MS FAB: For C₃₀H₄₀O₅N₇NaP requires 632.2726, found 632.2710.
HPLC: t_R 42.859 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Chlorophenyl-phosphorodichloridate

20 C₆H₄O₂P₁Cl₃, MW=246.43

Phosphorus oxychloride (2ml, 21.5mmol) was stirred with anhydrous diethylether (70ml) in a 250ml RBF. To this was added, dropwise, a solution of 4-chlorophanol (2.1ml, 21.5mmol), and anhydrous triethylamine (3.0ml, 21.5mmol) in anhydrous diethylether (30ml) at -80°C. This was stirred vigorously at -80°C for 1hr and left to rise to room temperature over 16hrs. The triethylamine hydrochloride salt was filtered off, and the filtrate reduced to dryness to give the crude product as a yellow oil (4.61g, 87.2%).

³¹P NMR: δ 4.99 (s).

¹³C NMR: δ 148.4 ('ipso'-Ph), 133.2 ('p'-Ph), 130.7 ('m'-Ph), 122.4 ('o'-Ph).

30 4-Chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate

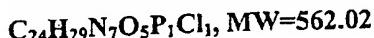
C₁₀H₁₂N₁O₄P₁Cl₂, MW=246.43

This was synthesised according to Standard Procedure 3, using L-Alanine methyl ester hydrochloride (2.61g, 18.7mmol) and p-chlorophenyl phosphorodichloridate (4.61g,

18.7mmol) and triethylamine (5.21ml, 37.4mmol) in anhydrous DCM (100ml). The usual workup yielded the crude product as a colourless crude oil (3.76g, 64.4%) which was stored in anhydrous THF (20ml) to give a 0.6M solution that was used without further purification.

- 5 ^{31}P NMR: δ 9.48, 9.25 (1:1).
 ^1H NMR: δ 7.36 (2H,d,J=8.20Hz,*'o'*-Ph), 7.32-7.22 (2H,m,*'m'*-Ph), 4.69 (1H,d,NHala), 4.27-4.15 (1H,m,CHala), 3.82 (3H,d,OCH₃), 1.56-1.53 (3H,dd,J=7.04Hz,CH₃ala).
 ^{13}C NMR: δ 173.4 (CO), 148.6 (*ipso*'-Ph), 131.9 (*'p'*-Ph), 130.3 (*'m'*-Ph), 122.3 (*'o'*-Ph), 53.2 (OCH₃), 50.9 (CHala), 20.9 (CH₃ala).

10 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-chlorophenyl-(methoxy-L-alaninyl)]-phosphate. CfI 620.



This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (250mg, 0.87mmol), tBuMgCl (1.75ml, 1.75mmol of a 1.0M solution in THF), and 4-chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (4.37ml, 2.62mmol, of a 0.6M solution in THF), in anhydrous THF (13ml) stirring at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ to give the pure product as white foamy solid

20 (364.5mg, 74.5%).

- 25 ^{31}P NMR: δ 4.01 (s).
 ^1H NMR: δ 7.42 (1H,d,H8), 7.22-7.17 (2H,m,*'m'*-Ph), 7.09-7.03 (2H,t,*'o'*-Ph), 5.99 (1H,d,H2'), 5.93 (1H,s,H3'), 5.83 (1H,bs,NHcPr), 5.45 (1H,bs,H1'), 4.96 (2H,bs,NH₂), 4.11 (2H,bs,H5'), 4.03-3.86 (1H,m,CHala), 3.62 (3H,s,OCH₃), 3.07 (1H,d,J=5.9Hz,H4'), 2.92 (1H,bs,CHcPr), 2.76-2.64 (1H,m,1of H6'), 1.64-1.59 (1H,t,1of H6'), 1.32-1.26 (3H,q,CH₃ala), 0.76 (2H,d,J=6.40Hz,2Hof CH₂cPr), 0.53 (2H,bs,2Hof CH₂cPr).
 ^{13}C NMR: δ 174.4 (CO), 160.4 (C2), 156.7 (C4), 151.3 (C6), 149.7 (*ipso*'-Ph), 136.7 (C2'), 135.9 (C8), 131.6 (C3'), 130.5 (*'p'*-Ph), 130.0 (*'m'*-Ph), 121.9 (*'o'*-Ph), 115.2 (C5), 69.4 (C5'), 59.25 (C1'), 52.9(OCH₃), 50.6 (CHala), 46.0 (C4'), 34.9 (C6'), 24.1 (CHcPr), 21.4 (CH₃ala), 7.8 (CH₂cPr).
HPLC: t_{R} 32.693, 33.012 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Bromophenyl-phosphorodichloridate

This was synthesised by a method analogous to that of 4-chlorophenyl-phosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 5 4-bromophenol (3.71g, 21.5mmol) in anhydrous diethylether (70ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (30ml). The reaction was stirred at -80°C to room temperature for 16hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (5.14g, 82.6%).

- ^{31}P NMR: δ 4.88 (s).
- 10 ^1H NMR: δ 7.63 (2H,d,J=8.14Hz, 'o'-Ph), 7.28 (2H,t, 'm'-Ph),
 ^{13}C NMR: δ 149.0 ('ipso'-Ph), 133.7 ('m'-Ph), 122.6 ('o'-Ph), 120.9 ('p'-Ph).

4-Bromophenyl-(methoxy-L-alaninyl)-phosphorochloridate

- 15 This was synthesised according to **Standard Procedure 3**, using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-bromophenyl-phoshorodichloridate (1.82g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (2.24g, 87.7%), which was stored in THF (12ml) to give a 0.524M solution.
- 20 ^{31}P NMR: δ 9.16, 9.10 (1:1).
 ^{13}C NMR: δ 173.4(CO), 150.1 ('ipso'-Ph), 133.3 ('m'-Ph), 122.7 ('o'-Ph), 119.6 ('p'-Ph), 53.3 (OCH₃), 51.0 (CHala), 20.9 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**25 O-[4-bromophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1710.**

- This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-bromophenyl-(methoxy-L-alaninyl)-phosphorochloridate (2.0ml, 1.05mmol, of a 0.524M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 4-6% MeOH in DCM, and then in 4% MeOH in DCM, to give the pure product as a white foamy solid (115.2mg, 54.4%).

³¹P NMR: δ 3.96 (s).

¹H NMR: δ 7.42 (1H,d,H8), 7.34-7.30 (2H,dd,J=8.73Hz,'o'-Ph), 7.03-6.97 (2H,t,J=8.68Hz,'m'-Ph), 6.02-5.97 (2H,m,H2'+NHcPr), 5.83-5.79 (1H,m,H3'), 5.43 (1H,t,H1'), 5.06 (2H,bs,NH₂), 4.28-4.04 (3H,m,H5'+NHala), 4.02-3.85 (1H,m,CHala), 3.61 (3H,d,OCH₂), 3.05 (1H,d,J=6.09Hz,H4'), 2.94 (1H,d,CHcPr), 2.75-2.66 (1H,m,1of H6'), 1.66-1.56 (1H,m,1of H6'), 1.31-1.25 (3H,dd,CH₃ala), 0.79-0.72 (2H,q,2Hof CH₂cPr), 0.54-0.49 (2H,t,2Hof CH₂cPr).

¹³C NMR: δ 174.4(CO), 160.3 (C2), 156.6 (C4), 151.3 (C6) 150.2 ('ipso'-Ph), 136.7 (C2'), 136.0 (C8), 133.0 ('m'-Ph), 131.6 (C3'), 122.4 ('o'-Ph), 118.1 ('p'-Ph), 115.2 (C5), 69.4 (C5'), 59.3 (C1'), 52.9 (OCH₃), 50.6 (CHala), 46.0 (C4'), 34.8 (C6'), 24.2 (CHcPr), 21.3 (CH₃ala), 7.8 (CH₂cPr).

MS ES⁺: m/z 606.13 (40%, M⁺), 628.1065 (100%, 79-M+Na⁺), 630.0967 (95%, 81-M+Na⁺).

MS FAB: For C₂₄H₂₉O₅N₇NaPBr requires 628.1049, found 628.1058, and C₂₄H₂₉O₅N₇NaP
15 ⁸¹Br requires 630.1028, found 630.1042.

HPLC: t_R 35.882 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Fluorophenyl-phosphorodichloridate

20 C₆H₄O₂P₁Cl₂F₁, MW=228.97

This was synthesised by a method analogous to that of 4-chlorophenyl-phosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-fluorophenol (2.41g, 21.5mmol) in anhydrous diethylether (70ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (30ml). The reaction was 25 stirred at -80°C for 4hrs, and then at room temperature for 2hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (4.08g, 83.0%).

³¹P NMR: δ 5.50 (s).

¹H NMR: δ 7.29-7.24 (2H,m,'o'-Ph), 7.09 (2H,t,J=8.29Hz,'m'-Ph),

¹³C NMR: δ 159.7('ipso'-Ph), 145.8 ('m'-Ph), 122.6 ('o'-Ph), 117.5 ('p'-Ph).

30

4-Fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate

C₁₀H₁₂N₁O₄P₁Cl₁F₁, MW=295.65

This was synthesised according to **Standard Procedure 3**, using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-fluorophenyl-phosphorodichloridate (1.64g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.97g, 93.0%), which was stored in THF (12ml) to give a

5 0.56M solution.

³¹P NMR: δ 9.84, 9.60 (1:1).

¹H NMR: δ 7.32-7.23 (2H,m,'o'-Ph), 7.12-7.06 (2H,m,'m'-Ph), 4.69 (1H,bs,NHala), 4.22 (1H,bs,CHala), 3.82 (3H,d,OCH₃), 1.57-1.53 (3H,m,CH₃ala).

¹³C NMR: δ 173.5(CO), 161.6 ('ipso'-Ph), 145.9 ('m'-Ph), 122.5 ('o'-Ph), 117.0 ('p'-Ph),
10 53.2 (OCH₃), 50.9 (CHala), 20.9 (CH₃ala).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[4-fluorophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1737.**

C₂₄H₂₉N₇O₅P₁F₁, MW=545.57

15 This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (1.89ml, 1.05mmol, of a 0.56M solution in THF), at room temperature for 24hrs. The solvent was removed under reduced pressure
20 and the residue columned in 2.5-5% methanol in chloroform, and then in 3% methanol in chloroform, to give the pure product as a pale yellow foamy solid (62.0mg, 32.5%).

³¹P NMR: δ 4.24, 4.23, 4.20, 4.19.

¹H NMR: δ 7.52 (1H,d,H8), 7.21-7.14 (2H,m,'o'-Ph), 7.03-6.97 (2H,m,'m'-Ph), 6.16 (1H,bs,NHcPr), 6.10-6.07 (1H,q,H2'), 5.93-5.89 (1H,q,H3'), 5.44 (1H,d,H1'), 5.14 (2H,bs,NH₂), 4.23-3.98 (4H,m,H5',NHala+CHala), 3.72 (3H,d,OCH₂), 3.16 (1H,d,J=6.03Hz,H4'), 3.03 (1H,d,CHcPr), 2.86-2.74 (1H,m,1of H6'), 1.76-1.66 (1H,m,1of H6'), 1.42-1.35 (3H,dd,CH₃ala), 0.89-0.83 (2H,q,2Hof CH₂cPr), 0.65-0.60 (2H,t,2Hof CH₂cPr).

¹³C NMR: δ 174.4(CO), 161.5 (C2), 160.3+156.6 ('p'-Ph), 156.6 (C4), 151.3 (C6) 150.2 (‘ipso'-Ph), 136.8 (C2'), 136.0 (C8), 131.6 (C3'), 121.9 ('o'-Ph), 115.1 (C5), 69.3 (C5'), 59.3 (C1'), 52.9 (OCH₃), 50.6 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 21.3 (CH₃ala), 7.8 (CH₂cPr).

HPLC: t_R 31.536 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Iodophenyl-phosphorodichloridate

5 $C_6H_4O_2P_1Cl_2I_1$, MW=336.07

This was synthesised by a method analogous to that of 4-chlorophenyl-phosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-iodophenol (4.72g, 21.5mmol) in anhydrous diethylether (60ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (20ml). The reaction was 10 stirred at -80°C for 4hrs, and then at room temperature for 2hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (6.2g, 85.8%).

^{31}P NMR: δ 4.72 (s).

1H NMR: δ 7.71 (2H,d,J=8.59Hz, 'o'-Ph), 7.06-7.02 (2H,dd,J=8.80Hz, 'm'-Ph),

^{13}C NMR: δ 149.9 ('*ipso*'-Ph), 139.8 ('*m*'-Ph), 122.9 ('*o*'-Ph), 91.9 ('*p*'-Ph).

15

4-Iodophenyl-(methoxy-L-alaninyl)-phosphorochloridate

$C_{10}H_{12}N_1O_4P_1Cl_1I_1$, MW=403.55

This was synthesised according to Standard Procedure 3, using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-iodophenyl-phoshorodichloridate (2.41g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (3.59g, >100%), which was stored in THF (14ml) to give a 0.51M solution.

^{31}P NMR: δ 9.31, 9.08 (1:1).

1H NMR: 7.74-7.69(2H,m,'o'-Ph), 7.32-7.05 (2H,m,'m'-Ph), 4.73 (1H,bs,NHala), 4.20

25 (1H,bs,CHala), 3.81 (3H,d,OCH₃), 1.56-1.53 (3H,dd,J=7.06Hz,CH₃ala).

^{13}C NMR: δ 173.4(CO), 149.9 ('*ipso*'-Ph), 139.5 ('*m*'-Ph), 123.0 ('*o*'-Ph), 90.4 ('*p*'-Ph), 53.3 (OCH₃), 50.9 (CHala), 20.9 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

30 **O-[4-iodophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1738.**

$C_{24}H_{29}N_7O_5P_1I_1$, MW=653.48

This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol),

tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-iodophenyl-(methoxy-L-alaninyl)-phosphorochloridate (2.05ml, 1.05mmol, of a 0.51M solution in THF), at room temperature for 48hrs. The solvent was removed under reduced pressure and the residue columned in 3-6% methanol in chloroform, and then in 3% methanol in 5 chloroform, to give the pure product as a white foamy solid (82.0mg, 29.9%).

³¹P NMR: δ 3.92 (s).

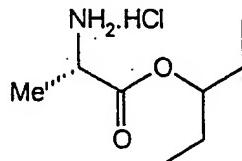
¹H NMR: δ 7.63-7.59 (2H,dd,J=8.65Hz,'m'-Ph), 6.98 (2H,t,J=8.20Hz'o'-Ph), 6.25 (1H,bs,NHcPr), 6.09 (1H,t,H2'), 5.91 (1H,t,H3'), 5.54 (1H,d,H1'), 5.21 (2H,bs,NH₂), 4.35-4.16 (3H,m,H5',NHala), 4.07-3.95 (1H,m,CHala), 3.71 (3H,d,OCH₃ala), 3.15 10 (1H,d,J=7.23Hz,H4'), 3.03 (1H,bs,CHcPr), 2.85-2.74 (1H,m,1of H6'), 1.76-1.65 (1H,m,1of H6'), 1.43-1.35 (3H,t,CH₃ala), 0.89-0.83 (2H,q,2Hof CH₂cPr), 0.63 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 174.4(CO) 160.2 (C2), 156.5 (C4), 151.1 (C6) 151.0 ('ipso'-Ph), 139.0 (C2'), 136.8 ('m'-Ph), 136.0 (C8), 131.5 (C3'), 122.8 ('o'-Ph), 115.0 (C5), 88.9 ('p'-Ph), 69.4 15 (C5'), 59.3 (C1'), 52.9 (OCH₃), 50.6 (CHala), 46.0 (C4'), 34.8 (C6'), 24.2 (CHcPr), 21.3 (CH₃ala), 7.8 (CH₂cPr).

HPLC: t_R 33.848 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

20 L-Alanine (3-pentyl) ester hydrochloride salt

25



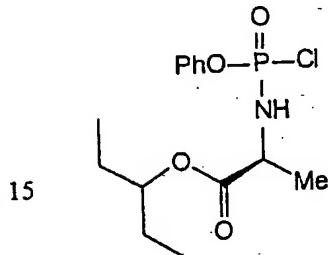
Thionyl chloride (1.6 ml, 0.022 M) was added dropwise to a stirred solution of 3-pentanol (18.2 ml, 0.17 M) at 0 °C under nitrogen. The mixture was stirred for 30 minutes, then 30 allowed to warm to room temperature. L-Alanine (pre-dried at 60 °C over P₂O₅ for 4 hrs: 1.0 g, 0.011 M) was added and the resulting suspension was heated at reflux overnight (the reaction mixture became a clear, colourless solution). The solvent was removed under reduced pressure to leave an oil which was repeatedly triturated and coevaporated with

diethyl ether, then petrol (60/80) to remove traces of 3-pentanol. The resulting oily residue solidified on drying under high vacuum to give a peach-coloured solid (1.96 g, 10 mmol, 89 %).

δ_H (²D-CH₃OH, 300 MHz) 0.94 (t, 6H, O-CH(CH₂CH₃)₂, J = 7), 1.57 (d, 3H, CH₃-ala, J = 7), 1.67 (m, 4H, O-CH(CH₂CH₃)₂, J = 7), 4.12 (q, 1H, CH-ala, J = 7), 4.88 [m, 1H, O-CH(C₂H₅)₂]; δ_C (²D-CH₃OH, 75 MHz) 8.87 [O-CH(CH₂CH₃)₂], 15.38 (CH₃-ala), 26.39, 26.44 [O-CH(CH₂CH₃)₂], 48.82 (CH-ala), 79.88 [O-CH(C₂H₅)₂], 170.03 (C=O).

Phenyl(3-pentyloxy-L-alaninyl)phosphorochloridate

10



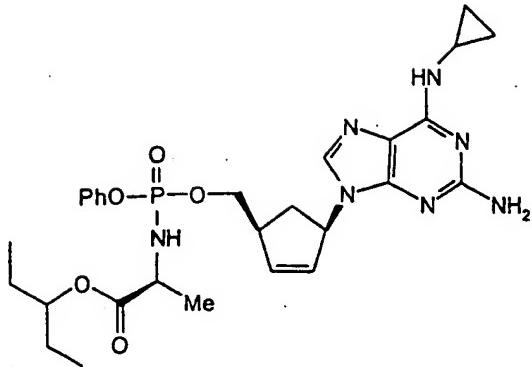
Prepared according to Standard Procedure 3, from phenyl-dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (3-pentyl) ester hydrochloride 20 salt 1a (0.583 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.055 g, >100 %).

δ_P (CDCl₃, 121 MHz) 8.99, 9.37

25 The product was redissolved in dry THF (5 ml) and used as a 0.211 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(3-pentyloxy-L-alaninyl)phosphate] [Cf 1685]

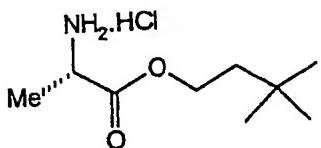
30



Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), $^3\text{BuMgCl}$ (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(3-pentyloxy-L-alaninyl)phosphor-o-chloridate 15 1b (3.3 ml of 0.211 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl_3) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using (i) MeOH: CHCl_3 (4:96) and (ii) MeOH: CHCl_3 (3:97) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.202 g, 0.35 mmol, 50 %).

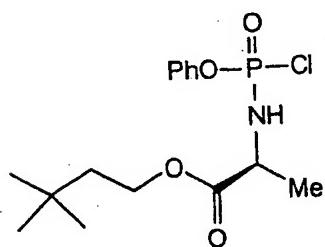
20 δ_{P} (CDCl_3 , 121 MHz) 3.89; δ_{H} (CDCl_3 , 300 MHz) 0.66 (m, 2H, $\text{CH}_2\text{-cPr}$), 0.90 [m, 8H, $\text{CH}_2\text{-cPr}$ and $\text{CH}(\text{CH}_2\text{CH}_3)_2$], 1.43 (m, 3H, $\text{CH}_3\text{-ala}$), 1.58 [m, 4H, $\text{CH}(\text{CH}_2\text{CH}_3)_2$], 1.72 (m, 1H, 6'H_a), 2.82 (m, 1H, 6'H_b), 3.05 (m, 1H, $\text{CH}\text{-cPr}$), 3.20 (m, 1H, 4'H), 3.77 (m, 1H, $\text{CH}\text{-ala}$), 4.05 (m, 1H, NH-ala), 4.22 (m, 2H, 5'H), 4.80 (m, 1H, O-CH-), 4.89 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.78 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 25 7.26 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_{C} (CDCl_3 , 75 MHz) 6.37 ($\text{CH}_2\text{-cPr}$), 8.50 [$\text{CH}(\text{CH}_2\text{CH}_3)_2$], 20.28 ($\text{CH}_3\text{-ala}$), 22.68 ($\text{CH}\text{-cPr}$), 25.28, 25.38 [$\text{CH}(\text{CH}_2\text{CH}_3)_2$], 33.51, 33.60 (6'C), 44.59, 44.69 (4'C), 49.40 ($\text{CH}\text{-ala}$), 57.79, 57.83 (1'C), 67.90 (5'C), 77.29 (OCH), 113.86 (5C), 119.10-119.18 (*o*-Ph), 123.84 (*p*-Ph), 128.61 (*m*-Ph), 130.09, 130.16 (3'C), 134.45, 134.56 (8C), 135.27, 135.41 (2'C), 149.66-149.93 (6C and *ipso*-Ph), 155.26 30 (4C), 158.95 (2C), 172.32, 172.44 (C=O); *m/z* (FAB) 584.2751 (MH^+ , $\text{C}_{28}\text{H}_{39}\text{N}_7\text{O}_5\text{P}$ requires 584.2750).

L-Alanine (3,3-dimethyl-1-butyl) ester hydrochloride salt



- 10 Prepared according to Standard Procedure 2, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), 3,3-dimethyl butan-1-ol (2.2 ml, 18 mmol) and toluene (100 ml). Conversion to the hydrochloride salt: the *p*-toluene sulfonate salt was redissolved in CHCl₃ and washed with 10 % potassium carbonate solution and water. The organic layer was dried (MgSO₄), filtered and the solvent was removed under reduced pressure to give the crude product as an oil. Aq. HCl (1 M), was added and the solution stirred for 30 minutes at room temperature. The solution was freeze-dried to give the hydrochloride salt as a white solid (3.31 g, 15.8 mmol, 88 %).
- 15 20 *δ*_H (*d*₄-CH₃OH, 300 MHz) 0.93 [s, 9H, O-(CH₂)₂(CH₃)₃], 1.50 (d, 3H, CH₃-ala, *J* = 7), 1.59 (t, 2H, O-CH₂CH₂, *J* = 7), 4.05 (q, 1H, CH-ala, *J* = 7), 4.25 (m, 2H, O-CH₂); *δ*_C (*d*₄-CH₃OH, 75 MHz) 15.18 (CH₃-ala), 28.91 [C(CH₃)₃], 29.54 [C(CH₃)₃], 41.62 (O-CH₂CH₂), 48.85 (CH-ala), 64.11 (O-CH₂CH₂-), 170.03 (C=O).

Phenyl(3,3-dimethyl-1-butoxy-L-alaninyl)phosphorochloridate



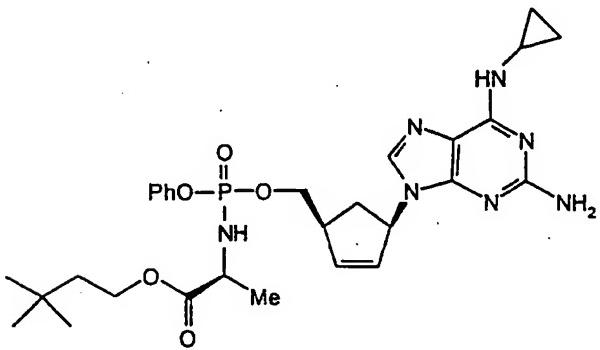
Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (3,3-dimethyl-1-butyl) ester hydro-chloride salt 2a (0.632 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.038 g, 99 %).

5 δ_P (CDCl₃, 121 MHz) 8.94, 9.30

The product was redissolved in dry THF (5 ml) and used as a 0.208 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

10 O-[phenyl(3,3-dimethyl-1-butoxy-L-alaninyl)phosphate [Cf 1687]



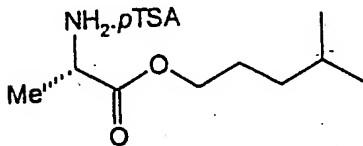
20

Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ³BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (3,3-dimethyl-1-butoxy-L-alaninyl) phosphorochloride 2b (3.5 ml of 0.208 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.287 g, 0.5 mmol, 69 %).

25 δ_P (CDCl₃, 121 MHz) 3.83; δ_H (CDCl₃, 300 MHz) 0.66 (m, 2H, CH₂-cPr), 0.90 (m, 2H, CH₂-cPr), 0.97 [s, 9H, C(CH₃)₃] 1.41 (m, 3H, CH₃-ala), 1.57 (m, 2H, O-CH₂CH₂), 1.74 (m, 1H, 6'H_a), 2.82 (m, 1H, 6'H_b), 3.05 (m, 1H, CH-cPr), 3.20 (m, 1H, 4'H), 3.70 (m, 1H, CH-ala), 4.04 (m, 1H, NH-ala), 4.22 (m, 4H, 5'H and O-CH₂CH₂), 4.88 (bs, 2H, NH₂), 5.57 (m, 1H, 1'H), 5.75 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 7.27 (m,

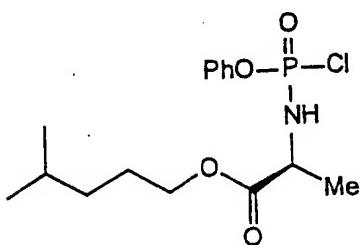
5H, ArH), 7.52 (d, 1H, 8H); δ_c (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 19.95, 20.01 (CH₃-ala), 22.69 (CH-cPr), 28.52 [C(CH₃)₃], 28.52 [C(CH₃)₃], 33.49, 33.57 (6'C), 40.59, 40.63 (OCH₂CH₂-), 44.58, 44.68 (4'C), 49.28 (CH-ala), 57.79, 57.83 (1'C), 62.28, 62.31 (OCH₂CH₂-), 67.86, 67.94 (5'C), 113.81 (5C), 119.10, 119.16 (*p*-Ph), 123.84 (*o*-Ph), 149.67-
5 128.61 (*m*-Ph), 130.10, 130.16 (3'C), 134.47, 134.56 (8C), 135.29, 135.40 (2'C), 149.67-
149.75 (6C and *ipso*-Ph), 155.25 (4C), 158.96 (2C), 172.55, 172.65 (C=O); *m/z* (FAB)
598.2896 (MH⁺, C₂₉H₄₁N₇O₅P requires 598.2907).

L-Alanine (4-methyl-1-pentyl) ester p-toluene sulfonate salt



15 Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), 4-methyl pentan-1-ol (2.24 ml, 18 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (6.082 g, 17.6 mmol, 98 %).
20 δ_H (d₄-CH₃OH, 300 MHz) 0.93 [d, 6H, CH(CH₃)₂], 1.27 (m, 2H, O-CH₂CH₂CH₂-), 1.54 (d, 3H, CH₃-ala), 1.59 [m, 1H, CH(CH₃)₂], 1.69 [m, 2H, O-(CH₂)₂CH₂], 2.39 (s, 3H, CH₃, p-TSA), 4.10 (m, 1H, CH-ala), 4.24 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, p-TSA), 21.83 (2H, ArH, *p*-TSA); δ_c (d₄-CH₃OH, 75 MHz) 15.23 (CH₃-ala), 20.31 (CH₃-*p*TSA), 21.83 [CH(CH₃)₂], 26.45 (O-CH₂CH₂CH₂-), 27.87 [CH(CH₃)₂], 34.93 (O-CH₂CH₂CH₂-), 48.85 (CH-ala), 66.77 [O-CH₂(CH₂)₂], 125.93 (*o*-Ph, *p*-TSA), 128.83 (*m*-Ph, *p*-TSA), 140.75
25 (*ipso*-C-CH₃, *p*-TSA), 142.39 (*ipso*-C-S, *p*-TSA), 170.07 (C=O).

Phenyl(4-methyl-1-pentyloxy-L-alaninyl)phosphorochloridate



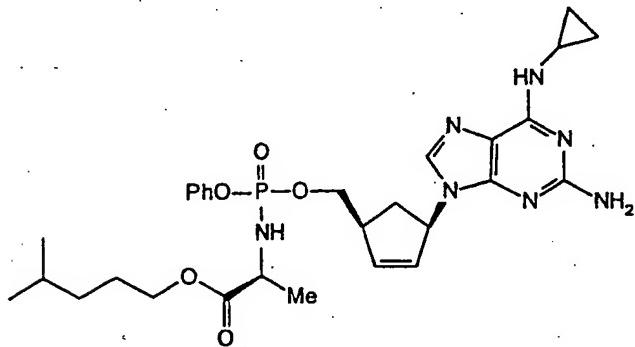
Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (4-methyl-1-pentyl) ester *p*-toluene sulfonate salt 3a (2.081 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.79 g, 85 %).

5 δ_P (CDCl₃, 121 MHz) 8.95, 9.31

The product was redissolved in dry THF (10 ml) and used as a 0.179 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

10 O-[phenyl (4-methyl-1-pentyloxy-L-alaninyl)phosphoryl] [Cf 1721]

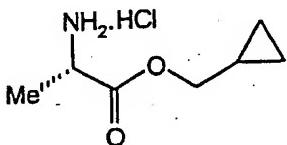


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), 'BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(4-methyl-1-pentyloxy-L-alaninyl)phosphor-25 ochloride 3b (4.1 ml of 0.179 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.288 g, 0.5 mmol, 69 %).

30 δ_P (CDCl₃, 121 MHz) 3.84, 3.88; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.24 [m, 2H, CH(CH₃)₂], 1.40 (t, 3H, CH₃-ala), 1.60 [m, 3H, CH(CH₃)CH₃], 1.73 [m, 3H, CH(CH₃)CH₃], 2.19 (m, 1H, 6'H_a), 2.80 (m, 1H, 6'H_b), 3.03 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.88 (m, 1H, CH-ala), 4.03 (m, 3H, OCH₂- and NH-

ala), 4.21 (m, 2H, 5'H), 4.99 (bs, 2H, NH₂), 5.55 (m, 1H, 1'H), 5.91 (m, 2H, NH-cPr and ala), 6.10 (m, 1H, 2'H), 7.29 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 7.79 (3'H), 11.55 (CH₃-ala), 21.61 [CH(CH₃)₂], 23.69 (CH-cPr), 25.66 (O-CH₂CH₂CH₂-), 29.63 [CH(CH₃)₂], 35.00 (6'C), 38.81 (O-CH₂CH₂CH₂-), 46.01, 46.11 (4'C), 50.72 (CH-5'ala), 59.21 (1'C), 69.31 (5'C), 69.85 (O-CH₂CH₂-), 115.25 (5C), 120.52-120.62 (*p*-Ph), 125.25 (*o*-Ph), 130.04 (*m*-Ph), 131.59 (3'C), 135.98 (8C), 136.71, 136.79 (2'C), 151.08, 151.17 (6C and *ipso*-Ph), 156.70 (4C), 160.40 (2C), 174.00, 174.10 (C=O); *m/z* (FAB) 598.2883 (MH⁺, C₂₉H₄₁N₇O₅P requires 598.2907).

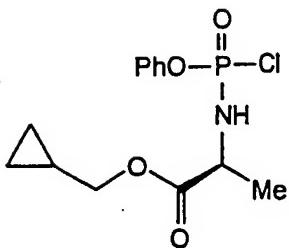
10 L-Alanine (cyclopropyl methyl) ester hydrochloride salt



Thionyl chloride (1.2 ml, 0.017 M) was added dropwise to a stirred solution of cyclopropyl methanol (6.8 ml, 8.4 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 minutes, then allowed to warm to room temperature. L-Alanine (pre-dried at 60 °C over 20 P₂O₅ for 4 hrs: 0.75 g, 8.4 mmol) was added and the resulting suspension was heated at reflux overnight (the reaction mixture became a clear, colourless solution). The solvent was removed under reduced pressure to leave an orange/red oil which was repeatedly triturated and coevaporated with diethyl ether, to remove traces of cyclopropyl methanol. Diethyl ether (~200 ml) was added and the mixture was stirred for 30 min. The resulting 25 suspension was filtered to give the product as a cream solid (1.29 g, 7.1 mmol, 85 %). δ_H (⁴D₄-CH₃OH, 300 MHz) 0.38 (m, 2H, CH₂-cPr), 0.65 (m, 2H, CH₂-cPr), 1.24 (m, 1H, CH-cPr), 1.60 (d, 3H, CH₃-ala, *J* = 7), 4.13 (m, 3H, CH-ala and O-CH₂); δ_C (⁴D₄-CH₃OH, 75 MHz) 4.17 (CH₂-cPr), 10.98 (CH-cPr), 16.72 (CH₃-ala), 50.33 (CH-ala), 72.70 (O-CH₂), 171.56 (C=O).

30

Phenyl(cyclopropyl methoxy-L-alaninyl)phosphorochloridate

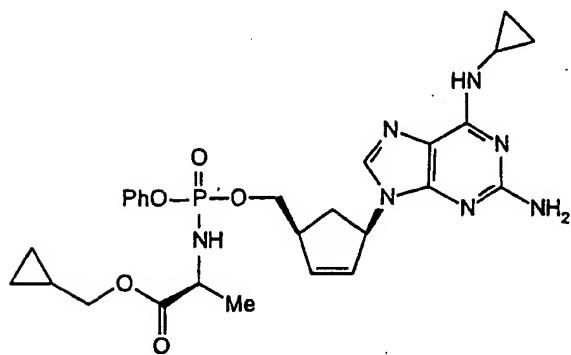


Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopropyl methyl) ester *p*-toluene sulfonate salt 4a (1.082 g, 6.0 mmol) and dry DCM (100 ml total). The crude
15 product was obtained as a clear, yellow oil (1.79 g, 94%).

δ_P (CDCl₃, 121 MHz) 9.00, 9.36

The product was redissolved in dry THF (5 ml) and used as a 0.385 g/ml solution.

20 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(cyclopropyl methoxy-L-alaninyl)]phosphate
[Cf 1774]

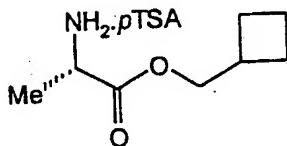


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), $^t\text{BuMgCl}$ (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclopropyl meth-oxy-L-alaninyl) phosphorochloridate 4b (1.85 ml of 0.385 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl_3) showed the reaction to be complete after 3.5 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl_3 (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.244 g, 0.4 mmol, 61%).

δ_p (CDCl_3 , 121 MHz) 3.88, 3.94; δ_H (CDCl_3 , 300 MHz) 0.29 (m, 2H, $\text{CH}_2\text{-cPr}$), 0.61 (m, 2H, $\text{CH}_2\text{-cPr}$), 0.87 (m, 2H, $\text{CH}_2\text{-cPr}$), 1.17 (m, 1H, $\text{CH}\text{-cPr}$), 1.42 (t, 3H, $\text{CH}_3\text{-ala}$), 1.69 (m, 1H, 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, $\text{CH}\text{-cPr}$), 3.18 (m, 1H, 4'H), 4.01 (m, 4H, $\text{OCH}_2\text{-}$, CH-ala and NH-ala), 4.21 (m, 2H, 5'H), 5.03 (bs, 2H, NH_2), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 6.05 (bs, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl_3 , 75 MHz) 2.24 ($\text{CH}_2\text{-cPr}$), 6.33 ($\text{CH}_2\text{-cPr}$), 8.66 ($\text{CH}_2\text{-cPr}$), 20.05, 20.11 (CH₃-ala), 22.68 (CH-cPr), 33.55 (6'C), 44.58, 44.68 (4'C), 49.24, 49.31 (CH-ala), 57.77, 57.82 (1'C), 67.76, 67.93 (O-CH₂), 69.27, 69.29 (5'C), 113.74 (5C), 119.10-119.19 (p-Ph), 123.84 (o-Ph), 128.61 (m-Ph), 130.09, 130.13 (3'C), 134.42, 134.50 (8C), 135.32, 135.40 (2'C), 149.66, 149.74 (6C and ipso-Ph), 155.26 (4C), 159.00 (2C), 172.64, 172.73 (C=O).

20

L-Alanine (cyclobutyl methyl) ester hydrochloride salt

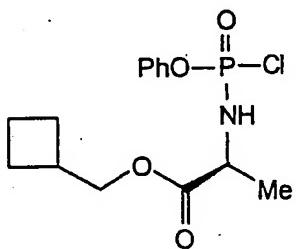


Prepared according to Standard Procedure 2, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclobutane methanol (1.9 ml, 20 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (4.249 g, 12.9 mmol, 72%).

δ_H ($d_4\text{-CH}_3\text{OH}$, 300 MHz) 1.54 (d, 3H, $\text{CH}_3\text{-ala}$, $J = 7$), 1.89 (m, 4H, cBu-2/4H), 2.08 (m, 2H, cBu-3H), 2.39 (s, 3H, CH_3 , *p*-TSA), 2.69 (9m, 1H, $\text{CH}\text{-cBu}$), 4.11 (q, 1H, $\text{CH}\text{-ala}$, $J = 7$), 4.22 (m, 2H, O-CH₂), 7.26 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -)

CH_3OH , 75 MHz) 16.7 (CH_3 -ala), 19.6 (CH_2 -cBu), 21.7 (CH_3 -*p*TSA), 25.9 (CH_2 -cBu), 35.7 (CH -cBu), 48.9 (CH -ala), 71.3 ($\text{O}-\text{CH}_2$), 127.4 (*o*-Ph, *p*-TSA), 130.3 (*m*-Ph, *p*-TSA), 142.2 (*ipso*-C-CH₃, *p*-TSA), 143.8 (*ipso*-C-S, *p*-TSA), 171.6 (C=O).

5 Phenyl(cyclobutyl methoxy-L-alaninyl)phosphorochloridate



15 Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclobutyl methyl) ester *p*-toluene sulfonate salt 5a (1.98 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (2.04 g, >100%).

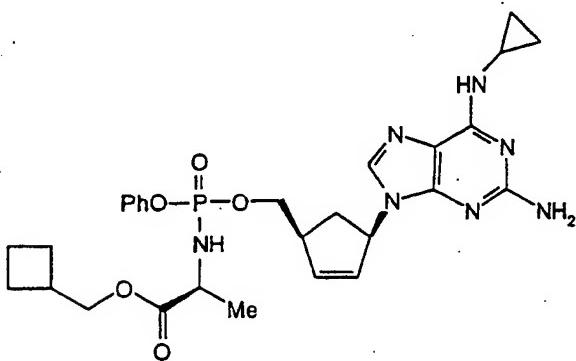
δ_{P} (CDCl₃, 121 MHz) 9.00, 9.34

20

The product was redissolved in dry THF (5 ml) and used as a 0.408 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(cyclobutyl methoxy-L-alaninyl)]phosphate

25 [Cf 1773]

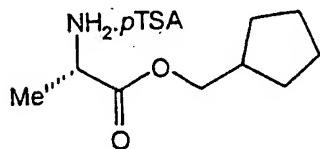


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl meth-oxy-L-alaninyl) phosphorochloride **5b** (1.7 ml of 0.408 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.213 g, 0.4 mmol, 52 %).

¹H NMR (¹³CDCl₃, 300 MHz) δ_P (CDCl₃, 121 MHz) 3.87, 3.91; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.89 (m, 2H, CH₂-cPr), 1.41 (t, 3H, CH₃-ala), 1.74 (m, 3H, CH₂-cBu and 6'H_a), 2.06 (m, 2H, CH₂-cBu), 2.61 (m, 2H, CH₂-cBu), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, cBu), 3.90 (m, 1H, NH-ala), 4.09 (m, 3H, OCH₂-, and CH-ala), 4.22 (m, 2H, 5'H), 4.98 (4'H), 5.56 (m, 1H, 1'H), 5.92 (m, 2H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (bs, 2H, NH₂), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 17.33 (CH₂-cBu), (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 17.33 (CH₂-cBu), 20.17, 20.23 (CH₃-ala), 22.68 (CH-cPr), 23.57 (2 × CH₂-cBu), 32.86 (CH-cBu), 33.51, 33.55 (6'C), 44.58, 44.68 (4'C), 49.23, 49.28 (CH-ala), 57.81, 57.85 (1'C), 67.78-67.94 (5'C), 68.17, 68.20 (O-CH₂), 113.83 (5C), 119.09-119.19 (*p*-Ph), 123.87 (*o*-Ph), 128.62 (*m*-Ph), 130.11, 130.15 (3'C), 134.51, 134.61 (8C), 135.30, 135.39 (2'C), 149.64-149.97 (6C and *ipso*-Ph), 155.20 (4C), 158.87 (2C), 172.64, 172.74 (C=O).

20

L-Alanine (cyclopentyl methyl) ester p-toluene sulfonate salt

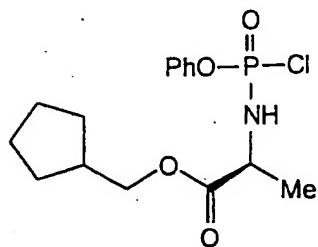


Prepared according to Standard Procedure 2, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclopentane methanol (1.9 ml, 18 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (6.21 g, 18 mmol, 100 %).

¹H NMR (¹³D₄-CH₃OH, 300 MHz) 1.22 (m, 2H, cPent 2/5H_a), 1.46 (d, 3H, CH₃-ala), 1.56 (m, 4H, cPent 2/3/4/5H_b), 1.70 (m, 2H, cPent 3/4H_a), 2.19 (m, 1H, CH-cPent), 2.31 (s, 3H, CH₃, *p*-

TSA), 4.06 (m, 3H, O-CH₂ and CH-ala), 7.18 (d, 2H, ArH, *p*-TSA), 7.64 (d, 2H, ArH, *p*-TSA); δ_C (¹³CH₃OH, 75 MHz) 15.25 (CH₃-ala), 20.30 (CH₃, *p*-TSA), 25.27 (CH₂-cPent), 29.10, 29.15 (CH₂-cPent), 38.72 (CH-cPent), 48.84 (CH-ala), 70.12 (O-CH₂), 125.93 (*o*-Ph, *p*-TSA), 128.82 (*m*-Ph, *p*-TSA), 140.75 (*ipso*-C-CH₃, *p*-TSA), 142.40 (*ipso*-C-S, *p*-TSA), 170.09 (C=O).

Phenyl(cyclopentyl methoxy-L-alaninyl)phosphorochloridate

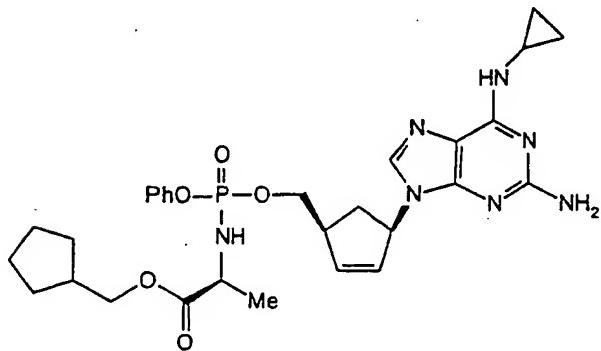


Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt **6a** (2.069 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, yellow oil (1.97 g, 95 %).

δ_P (CDCl₃, 121 MHz) 8.94, 9.30

The product was redissolved in dry THF (10 ml) and used as a 0.197 g/ml solution.

25 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(cyclopentyl methoxy-L-alaninyl)phosphate] [Cf 1722]

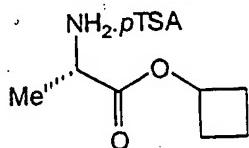


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), $^3\text{BuMgCl}$ (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (cyclopentane methoxy-L-alaninyl) phosphorochloridate **6b** (3.7 ml of 0.197 g/ml solution, 2.1 mmol) and dry THF (10 ml).

5 TLC (8 % MeOH in CHCl_3) showed the reaction to be complete after 3 hrs. The crude residue was purified by column chromatography, using MeOH: CHCl_3 (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.314 g, 0.5 mmol, 75 %).

δ_{P} (CDCl_3 , 121 MHz) 3.86, 3.87; δ_{H} (CDCl_3 , 300 MHz) 0.65 (m, 2H, $\text{CH}_2\text{-cPr}$), 0.89 [m, 10 8H, $\text{CH}_2\text{-cPr}$ and $(\text{CH}_2)_3\text{-cPent}$], 1.24 (m, 2H, $\text{CH}_2\text{-cPent}$), 1.41 (m, 3H, $\text{CH}_3\text{-ala}$), 1.65 (m, 2H, $\text{CH}\text{-cPent}$ and $6'\text{H}_a$), 2.81 (m, 1H, $6'\text{H}_b$), 3.04 (m, 1H, $\text{CH}\text{-cPr}$), 3.19 (m, 1H, $4'\text{H}$), 3.80 (m, 1H, $\text{CH}\text{-ala}$), 4.07 (m, 3H, OCH_2 and $\text{NH}\text{-ala}$), 4.22 (m, 2H, $5'\text{H}$), 4.92 (bs, 2H, NH_2), 5.55 (m, 1H, $1'\text{H}$), 5.81 (bs, 1H, $\text{NH}\text{-cPr}$), 5.92 (m, 1H, $3'\text{H}$), 6.11 (m, 1H, $2'\text{H}$), 7.26 (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_{C} (CDCl_3 , 75 MHz) 6.42 ($\text{CH}_2\text{-cPr}$), 21.43 ($\text{CH}_3\text{-ala}$), 22.73 ($\text{CH}\text{-cPr}$), 24.59 ($\text{CH}_2\text{-cPent}$), 25.35 ($\text{CH}_2\text{-cPent}$), 26.64 ($\text{CH}\text{-cPent}$), 33.43, 15 33.51 ($6'\text{C}$), 44.58, 44.68 ($4'\text{C}$), 49.23 ($\text{CH}\text{-ala}$), 57.86, 57.91 ($1'\text{C}$), 64.69, 64.97 (O-CH_2), 67.84 ($5'\text{C}$), 113.74 (5C), 119.09-119.18 (*p*-Ph), 123.88 (*o*-Ph), 128.62 (*m*-Ph), 130.05, 130.11 ($3'\text{C}$), 134.65, 134.76 (8C), 135.33, 135.44 (2'C), 149.63, 149.72 (6C and *ipso*-Ph), 154.98 (4C), 158.59 (2C), 172.50, 172.60 (C=O); *m/z* (FAB) 598.2745 (MH^+ , 20 $\text{C}_{29}\text{H}_{39}\text{N}_7\text{O}_5\text{P}$ requires 596.2750).

L-Alanine (cyclobutyl) ester p-toluene sulfonate salt



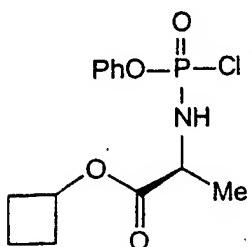
Prepared according to Standard Procedure 2, except using benzene as solvent: from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), cyclobutanol (0.9 ml, 11 mmol) and benzene (65 ml). The *p*-toluene sulfonate salt was isolated as a white solid (1.73 g, 5.5 mmol, 49 %).

δ_{H} ($d_4\text{-CH}_3\text{OH}$, 300 MHz) 1.51 (d, 3H, $\text{CH}_3\text{-ala}$, $J = 7$), 1.75 (m, 2H, $\text{CH}_2\text{-cBu}$), 2.14 (m, 2H, $\text{CH}_2\text{-cBu}$), 2.37 (m, 5H, $\text{CH}_2\text{-cBu}$ and $\text{CH}_3\text{-p-TSA}$), 4.05 (q, 1H, $\text{CH}\text{-ala}$, $J = 7$), 5.08

(m, 1H, CH-*c*Bu), 7.24 (d, 2H, ArH, *p*-TSA), 7.70 (d, 2H, ArH, *p*-TSA); δ_{C} (d_4 -CH₃OH, 75 MHz) 14.57 (CH₂-*c*Bu), 16.58 (CH₃-ala), 21.73 (CH₃-*p*TSA), 31.38, 31.44 (CH₂-*c*Bu), 50.16 (CH-ala), 72.47 (CH-*c*Bu), 127.35 (*o*-Ph, *p*-TSA), 130.23 (*m*-Ph, *p*-TSA), 142.13 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 170.71 (C=O).

5

Phenyl(cyclobutoxy-L-alaninyl)phosphorochloridate



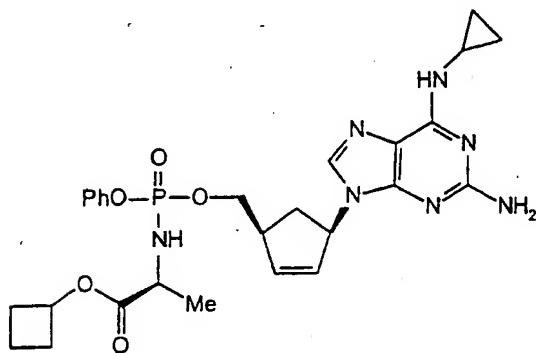
- 15 Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.75 ml, 5.0 mmol), dry triethylamine (1.4 ml, 10.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt **7a** (1.58 g, 5.0 mmol) and dry DCM (65 ml total). The crude product was obtained as a clear, colourless oil (1.13 g, 71 %).
 δ_{P} (CDCl₃, 121 MHz) 8.96, 9.33

20

The product was redissolved in dry THF (5 ml) and used as a 0.226 g/ml solution.

**(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
 O-[phenyl(cyclobutoxy-L-alaninyl)]phosphate [Cf 1775]**

25

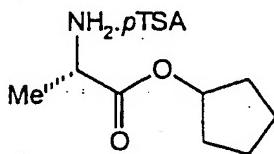


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), $^3\text{BuMgCl}$ (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl meth-oxy-L-alaninyl) phosphor-5-ochloride **7b** (2.95 ml of 0.226 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl_3) showed the reaction to be complete after 3.5 hrs. The crude residue was purified by column chromatography, using MeOH: CHCl_3 (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to a cream solid after trituration and coevaporation with diethyl ether (0.238 g, 0.4 mmol, 60 %).

10 δ_p (CDCl_3 , 121 MHz) 3.89, 3.93; δ_H (CDCl_3 , 300 MHz) 0.63 (m, 2H, $\text{CH}_2\text{-cPr}$), 0.87 (m, 2H, $\text{CH}_2\text{-cPr}$), 1.39 (m, 3H, $\text{CH}_3\text{-ala}$), 1.65 (m, 2H, $\text{CH}_2\text{-cBu}$), 1.81 (m, 1H, 6'H_a), 2.04 (m, 2H, $\text{CH}_2\text{-cBu}$), 2.36 (m, 2H, $\text{CH}_2\text{-cBu}$), 2.80 (m, 1H, 6'H_b), 3.03 (m, 1H, $\text{CH}\text{-cPr}$), 3.17 (m, 1H, 4'H), 3.97 (m, 2H, NH-ala and CH-ala), 4.18 (m, 2H, 5'H), 4.98 (m, 3H, NH₂ and OCH), 5.55 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 6.01 (m, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl_3 , 75 MHz) 7.80 ($\text{CH}_2\text{-cPr}$), 13.82 ($\text{CH}_2\text{-cBu}$), 21.42 ($\text{CH}_3\text{-ala}$), 22.06 ($\text{CH}\text{-cPr}$), 30.52-30.63 ($\text{CH}_2\text{-cBu}$), 35.01 (6'C), 46.01, 46.12 (4'C), 50.50 (CH-ala), 59.26 (1'C), 69.30 (CH-cBu), 70.19 (5'C), 115.25 (5C), 120.53, 120.59 (*p*-Ph), 125.28 (*o*-Ph), 130.05 (*m*-Ph), 131.53 (3'C), 135.97 (8C), 136.73, 136.85 (2'C), 151.08-151.17 (6C and *ipso*-Ph), 156.71 (4C), 160.44 (2C), 173.33 (C=O).

20

L-Alanine (cyclopentyl) ester p-toluene sulfonate salt



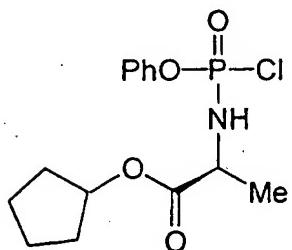
Prepared according to Standard Procedure 2, except using benzene as solvent: from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclopentanol (1.6 ml, 18 mmol) and benzene (100 ml). The *p*-toluene sulfonate salt was isolated as a beige solid (2.81 g, 8.5 mmol, 47 %).

δ_H ($d_4\text{-CH}_3\text{OH}$, 300 MHz) 1.51 (d, 3H, $\text{CH}_3\text{-ala}$, $J = 7$), 1.71 (m, 6H, $\text{CH}_2\text{-cPnt}$), 1.92 (m, 2H, $\text{CH}_2\text{-cPnt}$), 2.39 (m, 5H, $\text{CH}_2\text{-cBu}$ and CH_3 , *p*-TSA), 4.04 (q, 1H, CH-ala, $J = 7$), 5.28

(m, 1H, CH-*c*Pnt), 7.26 (d, 2H, ArH, *p*-TSA), 7.73 (d, 2H, ArH, *p*-TSA); δ_{C} (d_4 -CH₃OH, 75 MHz) 16.59 (CH₃-ala), 21.72 (CH₃-*p*TSA), 24.97 (CH₂-*c*Pnt), 33.81, 33.97 (CH₂-*c*Pnt), 50.31 (CH-ala), 81.37 (CH-*c*Pnt), 127.36 (*o*-Ph, *p*-TSA), 130.25 (*m*-Ph, *p*-TSA), 142.20 (*ipso*-C-CH₃, *p*-TSA), 143.79 (*ipso*-C-S, *p*-TSA), 171.17 (C=O).

5

Phenyl(cyclopentyloxy-L-alaninyl)phosphorochloridate

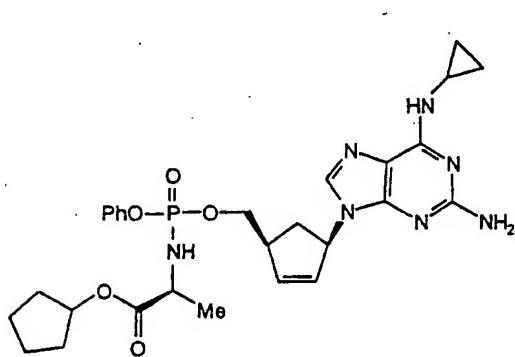


Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt 8a (1.98 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.8 g, 91 %).

δ_{P} (CDCl₃, 121 MHz) 9.01, 9.37

15 The product was redissolved in dry THF (5 ml) and used as a 0.361 g/ml solution.

**(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(cyclopentoxy-L-alaninyl)]phosphate [Cf 1776]**

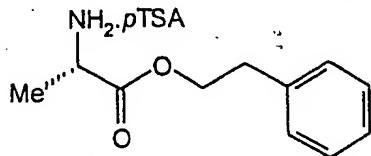


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl meth-oxy-L-alaninyl) phosphorochloride 8b (1.93 ml of 0.361 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.254 g, 0.4 mmol, 62 %).

¹H (CDCl₃, 121 MHz) 3.97, 3.98; ¹H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.38 (m, 3H, CH₃-ala), 1.67 (m, 7H, 3 × CH₂-cPent and 6'H_a), 1.86 (m, 2H, CH₂-cPent), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.96 (m, 2H, NH-ala and CH-ala), 4.21 (m, 2H, 5'H), 5.02 (bs, 1H, NH₂), 5.18 (m, 1H, OCH), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 5.98 (bs, 1H, NH-cPr), 6.11 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); ¹³C (CDCl₃, 75 MHz) 7.78 (CH₂-cPr), 21.42, 21.48 (CH₃-ala), 24.07 (CH-cPr), 32.91- (CH₂-cPent), 33.05, 33.08 (6'C), 34.97, 35.02 (CH₂-cPent), 46.02, 46.12 (4'C), 50.71 (CH-ala), 59.21, 59.25 (1'C), 69.22, 69.29 (5'C), 78.90 (OCH), 115.23 (5C), 120.55- 120.61 (*p*-Ph), 125.28 (*o*-Ph), 130.05 (*m*-Ph), 131.53, 131.59 (3'C), 135.87, 135.97 (8C), 136.73, 136.86 (2'C), 151.09, 151.18 (6C and *ipso*-Ph), 156.71 (4C), 160.44 (2C), 173.71, 173.80 (C=O).

20

L-Alanine (phenethyl) ester p-toluene sulfonate salt

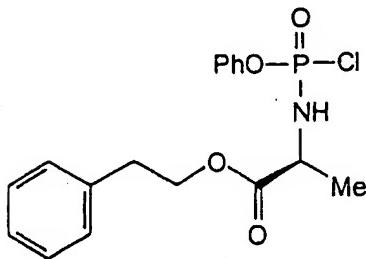


Prepared according to Standard Procedure 2, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), phenethyl alcohol (1.3 ml, 11 mmol) and toluene (65 ml). The *p*-toluene sulfonate salt was isolated as an off-white solid (4.0 g, 10.9 mmol, 97 %). ¹H (d₄-CH₃OH, 300 MHz) 1.46 (d, 3H, CH₃-ala; J = 7), 2.32 (2, 3H, CH₃, *p*-TSA), 2.93 (t, 2H, CH₂Ph, J = 7), 4.07 (q, 1H, CH-ala, J = 7), 4.37 (m, 2H, O-CH₂) 7.22 (m, 7H, ArH, *p*-

TSA and PhH), 7.78 (d, 2H, ArH, *p*-TSA); δ_c (d_4 -CH₃OH, 75 MHz) 16.80 (CH₃-ala), 22.06 (CH₃-*p*TSA), 36.20 (CH₂-Ph), 50.41 (CH-ala), 68.28 (O-CH₂), 127.70, 127.83 (*o*-Ar and *o*-Ph, *p*-TSA), 129.81 (*p*-Ar), 130.13, 130.48 (*m*-Ar and *m*-Ph, *p*-TSA), 139.23 (*ipso*-ArC), 142.30 (*ipso*-C-CH₃, *p*-TSA), 143.83 (*ipso*-C-S, *p*-TSA), 171.44 (C=O).

5

Phenyl(phenethoxy-L-alaninyl)phosphorochloridate



15 Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (phenethyl) ester *p*-toluene sulfonate salt 9a (1.232g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (1.16 g, 94 %).

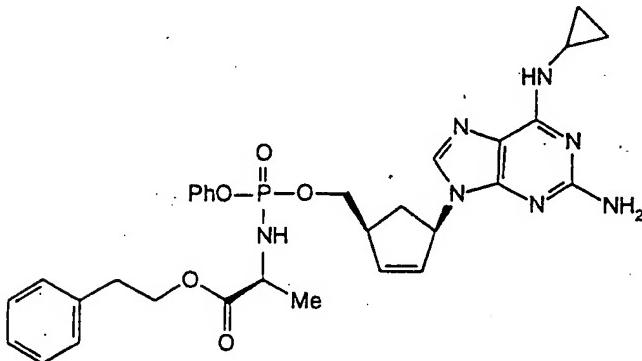
δ_p (CDCl₃, 121 MHz) 8.93, 9.25

20

The product was redissolved in dry THF (5 ml) and used as a 0.233 g/ml solution.

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(phenethoxy-L-alaninyl)]phosphate [Cf 1777]**

25



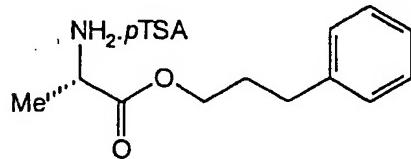
Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ¹BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(phenethoxy-L-alaninyl) phosphor-ochloride 9b (3.3 ml of 0.233 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to a cream solid after trituration and coevaporation with diethyl ether (0.181 g, 0.3 mmol, 42 %).

10 δ_{P} (CDCl₃, 121 MHz) 3.81, 3.86; δ_{H} (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.89 (m, 2H, CH₂-cPr), 1.35 (m, 3H, CH₃-ala), 1.71 (m, 1H, 6'H_a), 2.80 (m, 1H, 6'H_b), 2.96 (m, 2H, CH₂Ph), 3.03 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 3.91 (m, 2H, NH-ala and CH-ala), 4.18 (m, 2H, OCH), 4.36 (m, 2H, 5'H), 4.99 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.92 (m, 2H, 3'H and NH-cPr), 6.09 (m, 1H, 2'H), 7.26 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_{C} (CDCl₃, 75 MHz) 6.36 (CH₂-cPr), 19.98, 20.04 (CH₃-ala), 22.65 (CH-cPr), 33.46, 33.54 (6'C), 33.90 (CH₂-Ph), 44.56, 44.66 (4'C), 49.21 (CH-ala), 57.79, 57.85 (1'C), 64.84 (OCH₂), 67.82 (5'C), 113.79 (5C), 119.11- 119.17 (p-Ph), 123.87 (p-Ar), 125.68 (o-Ph), 127.53 (o-Ar), 127.83 (m-Ph), 128.62 (m-Ar), 130.07, 130.14 (3'C), 134.48 (8C), 135.30, 135.39 (2'C), 136.25 (ipso-Ar), 149.63, 149.71 (6C and ipso-Ph), 155.25 (4C), 158.94 (2C), 172.75, 172.45 (C=O).

15

20

L-Alanine (3-phenyl-1-propyl) ester p-toluene sulfonate salt



Prepared according to Standard Procedure 2, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 3-phenyl-1-propanol (1.5 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a yellow oil. Diethyl ether was added and the mixture was cooled for 30 mins. The resulting suspension was filtered to give the *p*-toluene sulfonate salt as a white solid (4.24 g, 11.2 mmol, 100 %).

30

δ_H (d_4 -CH₃OH, 300 MHz) 1.53 (d, 3H, CH₃-ala, $J = 7$), 1.97 (m, 2H, CH₂CH₂Ph), 2.34 (2, 3H, CH₃, *p*-TSA), 2.67 (t, 2H, CH₂Ph, $J = 7$), 4.10 (q, 1H, CH-ala, $J = 7$), 4.20 (t, 2H, O-CH₂, $J = 7$) 7.22 (m, 7H, ArH, *p*-TSA and PhH), 7.75 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 16.77 (CH₃-ala), 21.93 (CH₃-*p*TSA), 31.63 (CH₂CH₂-Ph), 33.37 (CH₂-Ph), 50.44 (CH-ala), 67.27 (O-CH₂), 127.26-127.58 (*o*-Ar and *o*-Ph, *p*-TSA), 129.66-130.00 (*p*-Ar), 130.41 (*m*-Ar and *m*-Ph, *p*-TSA), 142.31 (*ipso*-ArC), 142.82 (*ipso*-C-CH₃, *p*-TSA), 143.82 (*ipso*-C-S, *p*-TSA), 171.47 (C=O).

Phenyl(phenethoxy-L-alaninyl)phosphorochloridate

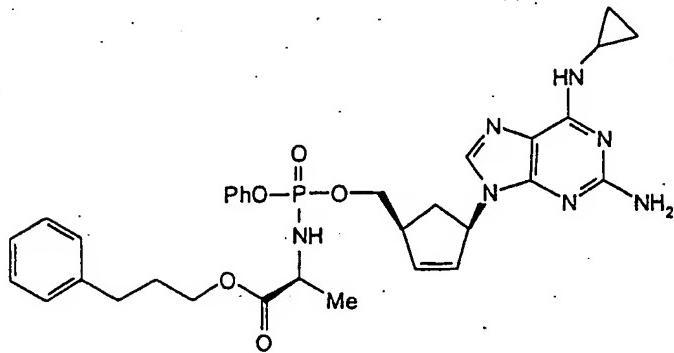
10

Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (3-phenyl-1-propyl) ester *p*-toluene sulfonate salt 9a (1.27g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale brown oil (1.16 g, 90 %).

15 δ_P (CDCl₃, 121 MHz) 8.94, 9.27

The product was redissolved in dry THF (5 ml) and used as a 0.231 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-phenyl-1-propoxy-L-alaninyl)]phosphate [Cf 1778]

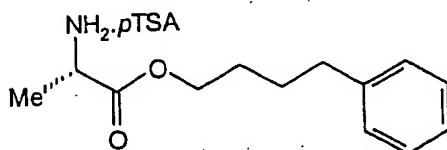


30 Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), 'BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-phenyl-1-propoxy-L-alaninyl) phosphorochloridate 10b (3.5 ml of 0.231 g/ml solution, 2.1 mmol) and dry THF (8 ml).

TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 4 hrs. The crude residue was purified three times by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.330 g, 0.5 mmol, 75 %).

- 5 δ_p (CDCl₃, 121 MHz) 3.89, 3.91; δ_H (CDCl₃, 300 MHz) 0.63 (m, 2H, CH₂-cPr), 0.88 (m, 2H, CH₂-cPr), 1.42 (m, 3H, CH₃-ala), 1.72 (m, 1H, 6'H_a), 1.98 (CH₂CH₂Ph), 2.69 (CH₂Ph), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.07 (m, 6H, NH-ala, CH-ala, OCH and 5'H), 5.00 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.91 (m, 2H, 3'H and NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_c (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 20.06, 20.12 (CH₃-ala), 22.65 (CH-cPr), 29.02 (CH₂CH₂Ph), 30.97 (CH₂Ph), 33.48, 33.55 (6'C), 44.57, 44.67 (4'C), 49.26 (CH-ala), 57.78, 57.84 (1'C), 10 125.09 (*o*-Ar), 127.33, 127.47 (*m*-Ph), 128.63 (*m*-Ar), 130.10, 130.17 (3'C), 134.47, 134.58 (8C), 135.27, 135.37 (2'C), 139.81 (*ipso*-Ar), 149.65, 149.74 (6C and *ipso*-Ph), 15 155.27 (4C), 158.98 (2C), 172.49, 172.58 (C=O).

L-Alanine (4-phenyl-1-butyl) ester p-toluene sulfonate salt



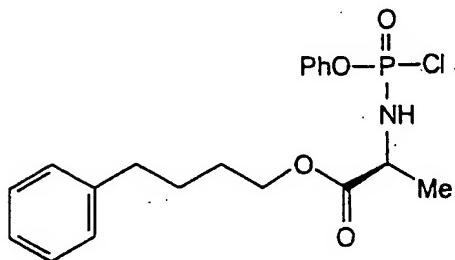
Prepared according to Standard Procedure 2, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 4-phenyl-1-butanol (1.7 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a clear, colourless oil, which solidified to a white solid after trituration and coevaporation with petrol (60/80) (4.4 g, 11.2 mmol, 100 %).

- 25 δ_H (*d*₄-CH₃OH, 300 MHz) 1.55 (d, 3H, CH₃-ala, *J* = 7), 1.74 (m, 4H, -(CH₂)₂CH₂Ph), 2.41 (2, 3H, CH₃, *p*-TSA), 2.67 (m, 2H, CH₂Ph), 4.12 (q, 1H, CH-ala, *J* = 7), 4.28 (m, 2H, O-CH₂) 7.25 (m, 7H, ArH, *p*-TSA and PhH), 7.75 (d, 2H, ArH, *p*-TSA); δ_c (*d*₄-CH₃OH, 75 MHz) 16.65 (CH₃-ala), 21.74 (CH₃-*p*-TSA), 29.18, 29.50 (OCH₂(CH₂)₂CH₂-Ph), 36.72 (CH₂-Ph), 50.27 (CH-ala), 67.74 (O-CH₂), 127.31, 127.36 (*o*-Ar and *o*-Ph, *p*-TSA), 129.79

(*p*-Ar), 130.25 (*m*-Ar and *m*-Ph, *p*-TSA), 142.14 (*ipso*-ArC), 143.64, 143.87 (*ipso*-C-CH₃ and *ipso*-C-S, *p*-TSA), 171.47 (C=O).

Phenyl(4-phenyl-1-butoxy-L-alaninyl)phosphorochloridate

5



- 15 Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (4-phenyl-1-butyl) ester *p*-toluene sulfonate salt 11a (1.32g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale brown oil (1.13 g, 85 %).

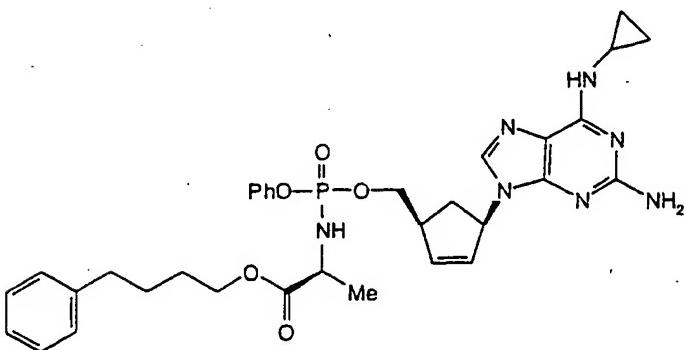
δ_P (CDCl₃, 121 MHz) 8.89, 9.24

20

The product was redissolved in dry THF (5 ml) and used as a 0.226 g/ml solution.

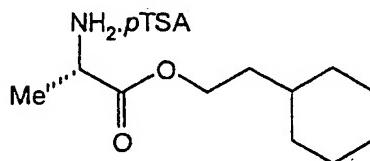
(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(4-phenyl-1-butoxy-L-alaninyl)]phosphate [Cf 1779]

25



- Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), 'BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(4-phenyl-1-butoxy-L-alaninyl) phosphorochloridate 11b (3.7 ml of 0.226 g/ml solution, 2.1 mmol) and dry THF (8 ml).
- 5 TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 4 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.314 g, 0.5 mmol, 69 %).
- δ_P (CDCl₃, 121 MHz) 3.87, 3.90; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.87 (m, 10 2H, CH₂-cPr), 1.41 (m, 3H, CH₃-ala), 1.71 (m, 5H, (CH₂)₂CH₂Ph and 6'H_a), 2.65 (m, 2H, CH₂Ph), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 4.06 (m, 6H, NH-ala, CH-ala, 5'H and OCH₂-) 5.02 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.90 (m, 1H, 3'H), 5.98 (bs, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 20.05, 20.11 (CH₃-ala), 22.65 (CH-cPr), 26.51 15 (CH₂CH₂CH₂Ph), 27.02 (CH₂(CH₂)₂Ph), 33.48, 33.55 (6'C), 34.32 (CH₂Ph), 44.56, 44.67 (4'C), 49.22, 49.26 (CH-ala), 57.79, 57.83 (1'C), 64.40 (OCH₂), 67.86, 67.94 (5'C), 113.75 (5C), 119.10, 119.15 (*p*-Ph and *p*-Ar), 123.85 (*o*-Ph), 124.88 (*o*-Ar), 127.33, 127.35 (*m*-Ph), 128.61 (*m*-Ar), 130.07, 130.12 (3'C), 134.44, 134.54 (8C), 135.30, 135.39 (2'C), 140.76 (*ipso*-Ar), 149.64-149.87 (6C and *ipso*-Ph), 155.26 (4C), 158.98 (2C); 20 172.53, 172.63 (C=O).

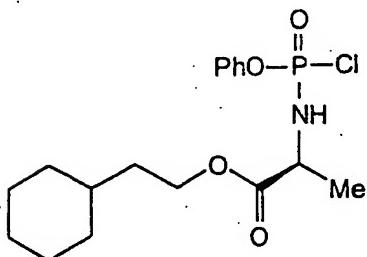
L-Alanine (2-cyclohexyl ethyl) ester p-toluene sulfonate salt



- Prepared according to Standard Procedure 2, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 2-cyclohexyl ethanol (1.56 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a clear, colourless oil, which solidified to a white solid after trituration and coevaporation with diethyl ether (2.8 g, 7.5 mmol, 67 %).

δ_H (d_4 -CH₃OH, 300 MHz) 0.97 (m, 2H, CH₂), 1.24 (m, 4H, 2 \times CH₂), 1.42 (m, 1H, CH-cHx), 1.54 (d, 3H, CH₃-ala, J = 7), 1.63 (m, 2H, CH₂), 1.75 (m, 4H, 2 \times CH₂), 2.39 (s, 3H, CH₃, *p*-TSA), 4.09 (q, 1H, CH-ala, J = 7), 4.28 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 16.65 (CH₃-ala), 21.74 (CH₃-*p*TSA), 27.68 (CH₂), 27.93 (CH₂), 34.58 (CH₂), 34.62 (CH₂), 36.10 (CH-cHx), 50.27 (CH-ala), 66.05 [O-CH₂(CH₂)₂], 127.36 (*o*-Ph, *p*-TSA), 130.24 (*m*-Ph, *p*-TSA), 142.13 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(2-cyclohexyl ethoxy-L-alaninyl)phosphorochloridate

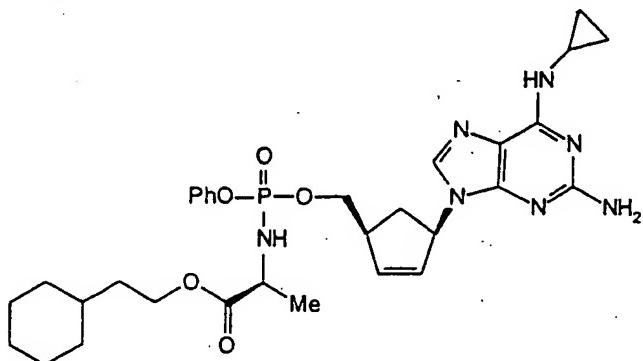


Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclohexyl ethyl) ester *p*-toluene sulfonate salt 12a (2.24g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.86 g, 83 %).

δ_P (CDCl₃, 121 MHz) 8.96, 9.31

The product was redissolved in dry THF (5 ml) and used as a 0.372 g/ml solution.

25 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(2-cyclohexyl-1-ethoxy-L-alaninyl)]phosphate [Cf 1780]



Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ³BuMgCl (1.0 M in THF: 1.4 ml; 1.4 mmol) phenyl(cyclohexyl ethoxy-L-alaninyl) phosphorochloride 12b (2.1 ml of 0.372 g/ml solution, 2.1 mmol) and dry THF (8 ml).

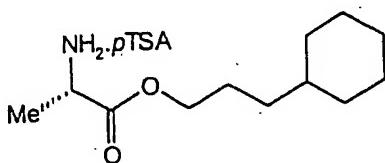
5 TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.302 g, 0.5 mmol, 69 %).

10 δ_P (CDCl₃, 121 MHz) 3.91, 3.94; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.91 (m, 4H, CH₂ and CH₂-cPr), 1.21 (m, 2H, CH₂), 1.41 (m, 3H, CH₃-ala), 1.52 (m, 2H, CH-cHx and 6'H_a), 1.70 (m, 6H, 3 × CH₂), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.10 (m, 6H, NH-ala, CH-ala, OCH₂ and 5'H), 5.03 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.96 (m, 1H, 3'H), 5.98 (m, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, Ar), 7.51 (5C), 119.10-119.19 (*p*-Ph), 123.85 (*o*-Ph), 128.61 (*m*-Ph), 130.12 (3'C), 134.44, 134.54 (8C), 135.28, 135.38 (2'C), 149.66-149.94 (6C and *ipso*-Ph), 155.28 (4C), 155.99 (2C), 172.57, 172.66 (C=O).

15

20

L-Alanine (3-cyclohexyl-1-propyl) ester p-toluene sulfonate salt

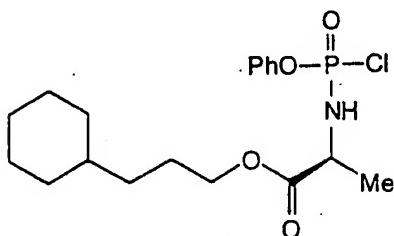


Prepared according to Standard Procedure 2, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 3-cyclohexyl-1-propanol (1.7 ml, 11 mmol) and toluene (65 ml). The solvent was removed and diethyl ether was added. The resulting suspension was filtered to give the product as a white solid (3.9 g, 10.1 mmol, 90 %).

30 δ_H (d₄-CH₃OH, 300 MHz) 0.92 (m, 2H, CH₂), 1.23 (m, 6H, 3 × CH₂), 1.54 (d, 3H, CH₃-ala, J = 7), 1.71 (m, 7H, CH-cHx and 3 × CH₂), 2.39 (s, 3H, CH₃, *p*-TSA), 4.10 (q, 1H,

CH -ala, $J = 7$), 4.22 (m, 2H, O- CH_2), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_c (d_4 - CH_3OH , 75 MHz) 16.66 (CH_3 -ala), 21.74 (CH_3 -*p*TSA), 27.36 (CH_2), 27.83 (CH_2), 28.11 (CH_2), 34.80 (CH_2), 34.90 (CH_2), 39.03 (CH-cHx), 50.27 (CH-ala), 68.27 (OCH_2), 127.36 (*o*-Ph, *p*-TSA), 130.24 (*m*-Ph, *p*-TSA), 142.12 (*ipso*-C- CH_3 , *p*-TSA), 5 143.89 (*ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(3-cyclohexyl-1-propoxy-L-alaninyl)phosphorochloridate

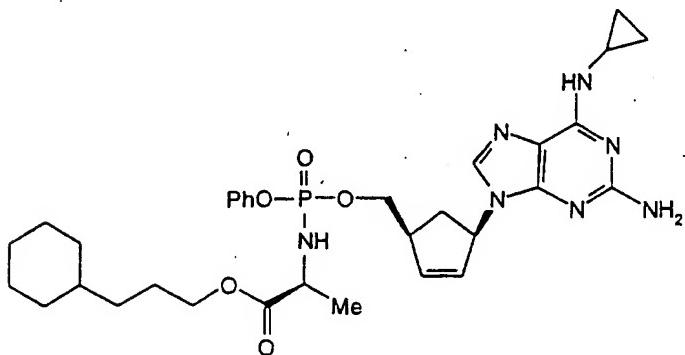


Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (3-cyclohexyl-1-propyl) ester *p*-toluene sulfonate salt 13a (2.32g, 6.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (2.31 g, 99 %).

20 δ_p (CDCl_3 , 121 MHz) 8.99, 9.35

The product was redissolved in dry THF (5 ml) and used as a 0.463 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
25 O-[phenyl(3-cyclohexyl-1-propoxy-L-alaninyl)]phosphate [Cf 1781]

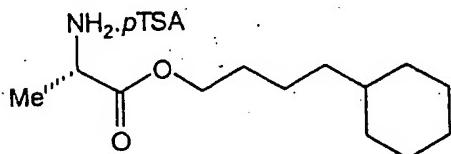


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), *t*BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-cyclohexyl-1-propoxy-L-alaninyl) phosphorochloridate 13b (1.8 ml of 0.463 g/ml solution, 2.1 mmol) and dry THF (8 ml).
5 TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2.5 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.276 g, 0.4 mmol, 62 %).

δ_{P} (CDCl₃, 121 MHz) 3.89, 3.91; δ_{H} (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.89 (m, 10 2H, CH₂-cPr), 1.21 (m, 6H, 3 × CH₂), 1.41 (m, 3H, CH₃-ala), 1.66 (m, 8H, CH-cHx, 3 × CH₂ and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.04 (m, 6H, NH-ala, CH-ala, OCH₂ and 5'H), 4.98 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, Ar), 7.57 (d, 1H, 8H); δ_{C} (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 20.09, 20.15 (CH₃-ala), 22.66 (CH-cPr), 24.85 (CH₂), 25.27 (CH₂), 25.55 15 (CH₂), 29.92 (CH₂), 32.20, 32.33 (6'C), 33.49, 33.57 (CH-cHx), 36.22 (CH₂), 44.58, 44.68 (4'C), 49.27 (CH-ala), 57.78, 57.83 (1'C), 65.01 (OCH₂), 67.84 (5'C), 113.86 (5C), 119.10-119.19 (*p*-Ph), 123.85 (*o*-Ph), 128.61 (*m*-Ph), 130.12 (3'C), 134.47, 134.57 (8C), 135.28, 135.38 (2'C), 149.65-149.74 (6C and *ipso*-Ph), 155.27 (4C), 158.96 (2C), 172.53, 172.64 (C=O).

20

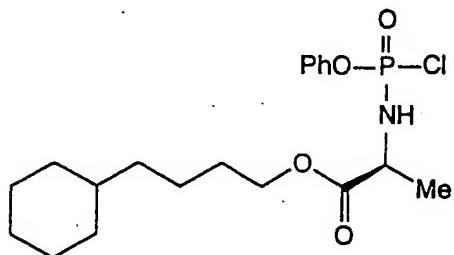
L-Alanine (4-cyclohexyl-1-butyl) ester *p*-toluene sulfonate salt



Prepared according to Standard Procedure 2, from L-alanine (0.51 g, 5.8 mmol), *p*-TSA
30 monohydrate (1.21 g, 6.3 mmol), 4-cyclohexyl-1-butanol (1.0 ml, 5.8 mmol) and toluene (65 ml). The *p*-toluene sulfonate salt was obtained as a white crystalline solid (2.15 g, 5.4 mmol, 93 %).

- δ_H (d_4 -CH₃OH, 300 MHz) 0.92 (m, 2H, CH₂), 1.17 (m, 6H, 3 \times CH₂), 1.39 (m, 2H, CH₂), 1.54 (d, 3H, CH₃-ala, J = 7), 1.69 (m, 7H, CH-cHx and 3 \times CH₂), 2.39 (s, 3H, CH₃, *p*-TSA), 4.10 (q, 1H, CH-ala, J = 7), 4.24 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 16.66 (CH₃-ala), 21.74
- 5 (CH₃-*p*TSA), 24.51 (CH₂), 27.89 (CH₂), 28.18 (CH₂), 30.25 (CH₂), 34.90 (CH₂), 38.59 (CH₂), 39.27 (CH-cHx), 50.27 (CH-ala), 67.94 (OCH₂), 127.36 (*o*-Ph, *p*-TSA), 130.23 (*m*-Ph, *p*-TSA), 142.15 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(4-cyclohexyl-1-butoxy-L-alaninyl)phosphorochloridate

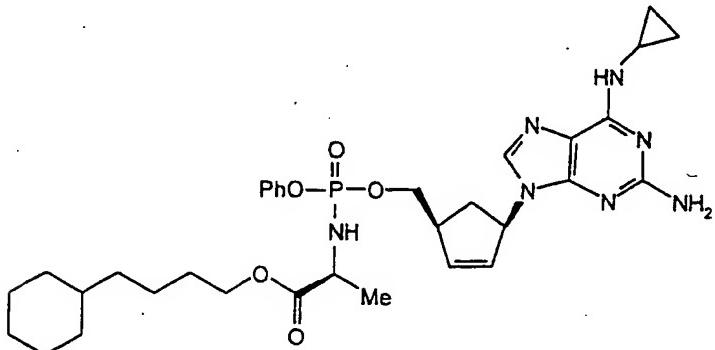


Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (4-cyclohexyl-1-butyl) ester *p*-toluene sulfonate salt 14a (1.2g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, brown oil (1.36 g, >100 %).

δ_P (CDCl₃, 121 MHz) 8.91, 9.28

The product was redissolved in dry THF (5 ml) and used as a 0.272 g/ml solution.

- 25 (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(4-cyclohexyl-1-butoxy-L-alaninyl)]phosphate [Cf 1782]



WO 00/18775

76

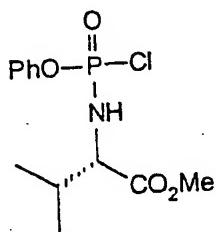
Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-cyclohexyl-1-propoxy-L-alaninyl) phosphorochloridate 14b (3.1 ml of 0.272 g/ml solution, 2.1 mmol) and dry THF (8 ml).

5 TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.341 g, 0.5 mmol, 75 %).

10 δ_p (CDCl₃, 121 MHz) 3.89, 3.91; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.86 (m, 2H, CH₂-cPr), 1.21 (m, 8H, 4 × CH₂), 1.41 (m, 3H, CH₃-ala), 1.65 (m, 8H, CH-cHx, 3 × CH₂ and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, 4'H), 4.04 (m, 6H, NH-ala, CH-ala, OCH₂ and 5'H), 4.96 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.92 (m, 1H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, Ar), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 20.10, 20.16 (CH₃-ala), 22.00 (CH₂), 22.65 (CH-cPr), 25.34 (CH₂), 25.64 (CH₂-cPr), 27.77 (CH₂), 32.28 (CH-cHx), 33.48, 33.56 (6'C), 36.45 (CH₂), 44.58, 44.68 (4'C), 49.24 (CH-ala), 57.79, 57.84 (1'C), 64.69 (OCH₂), 67.84, 67.94 (5'C), 113.86 (5C), 119.10-119.19 (*p*-Ph), 123.86 (*o*-Ph), 128.62 (*m*-Ph), 130.11, 130.17 (3'C), 134.47, 134.57 (8C), 135.28, 135.39 (2'C), 149.65-149.74 (6C and *ipso*-Ph), 155.26 (4C), 158.96 (2C), 172.54, 172.64 (C=O).

20

Phenyl(methoxy-L-valinyl)phosphorochloridate



30

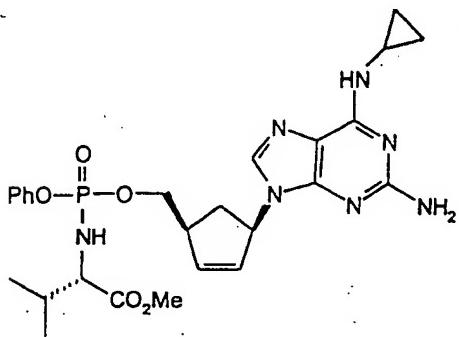
Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-valine methyl ester hydrochloride salt

(0.5 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (0.922 g, >100 %).

δ_P (CDCl₃, 121 MHz) 8.99, 9.37

- 5 The product was redissolved in dry THF (5 ml) and used as a 0.184 g/ml solution.

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[phenyl(methoxy-L-valinyl)phosphosphate [Cf 1686]**

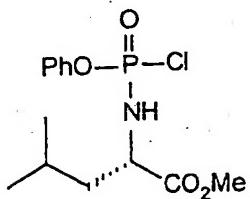


- Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ³BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(methoxy valinyl)phosphorochloridate 15a (3.5 ml of 0.184 g/ml solution, 2.1 mmol) and dry THF (5 ml). The reaction mixture was stirred for 16 hrs, after which time a further 1.5 ml of the solution of 15a was added. The reaction mixture was stirred for a further 4 hrs. The crude residue was purified by column chromatography, using MeOH:DCM (5:95) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.161 g, 0.3 mmol, 41 %).

δ_P (CDCl₃, 121 MHz) 4.65, 4.74; δ_H (CDCl₃, 300 MHz) 0.66 (m, 2H, CH₂-cPr), 0.94 [m, 8H, CH₂-cPr and CH(CH₃)₂], 1.71 (m, 1H, 6'H_a), 2.06 [m, 1H, CH(CH₃)₂], 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.52 (m, 1H, CH-val), 3.70 (d, 3H, OCH₃), 3.83 (m, 1H, NH-val), 4.22 (m, 2H, 5'H), 4.86 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.74 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.11 (m, 1H, 2'H), 7.27 (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 16.36, 16.45 [CH(CH₃)₂], 22.65 (CH-cPr),

31.08, 31.16 [CH(CH₃)₂], 33.61 (6'C), 44.60, 44.70 (4'C), 51.05, 51.10 (OCH₃), 57.78 (1'C), 58.96, 59.01 (CH-val), 67.90 (5'C), 113.91 (5C), 119.03-119.13 (*o*-Ph), 123.80 (*p*-Ph), 128.58 (*m*-Ph), 130.05, 130.14 (3'C), 134.47 (8C), 135.27, 135.39 (2'C), 149.66-149.84 (6C and *ipso*-Ph), 155.28 (4C), 158.96 (2C), 172.10, 172.19 (C=O); *m/z* (FAB) 5 556.2428 (MH⁺, C₂₆H₃₅N₇O₅P requires 556.2437).

Phenyl(methoxy-L-leucinyl)phosphorochloridate



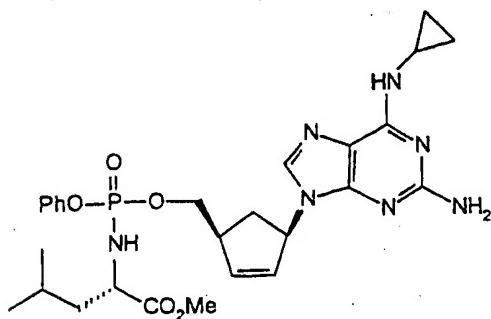
15

Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.41 ml, 2.8 mmol), dry triethylamine (0.77 ml, 5.5 mmol), L-leucine methyl ester hydrochloride salt (0.5 g, 2.8 mmol) and dry DCM (60 ml total). The crude product was obtained as a 20 clear, pale yellow oil (1.062 g, >100 %).

δ_P (CDCl₃, 121 MHz) 9.33, 9.51

The product was redissolved in dry THF (5 ml) and used as a 0.212 g/ml solution.

25 (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-leucinyl)phosphate] [Cf 1718]

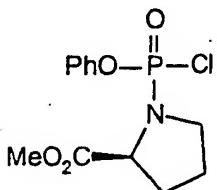


Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol 0.2 g, 0.7 mmol), 'BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (methoxy-L-leucinyl) phosphoro-chloridate 16a (3.2 ml of 0.212 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.211 g, 0.4 mmol, 53 %).

δ_P (CDCl₃, 121 MHz) 3.98, 4.06; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.89 [m, 10 8H, CH₂-cPr and CH(CH₃)₂], 1.51 (m, 2H, CH₂-leu), 1.69 [(m, 2H, CH(CH₃)₂ and 6'H_a], 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.16 (m, 1H, 4'H), 3.67 (m, 1H, CH-leu), 3.69 (d, 3H, OCH₃), 3.98 (m, 1H, NH-leu), 4.19 (m, 2H, 5'H), 4.97 (bs, 2H, NH₂), 5.55 (m, 1H, 1'H), 5.91 (m, 1H, NH-cPr and 3'H), 6.09 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 20.69, 20.82 (CH₃-leu), 22.69 (CH-cPr), 23.28, 15 23.41 [CH(CH₃)₂], 33.54 (6'C), 42.60-42.81 (CH₂-leu), 44.59, 44.70 (4'C), 51.19, (OCH₃), 52.07, 52.16 (CH-leu), 57.80 (1'C), 67.91, 67.98 (5'C), 113.88 (5C), 118.99-119.14 (*o*-Ph), 123.80 (*p*-Ph), 128.58 (*m*-Ph), 130.06, 130.14 (3'C), 134.53 (8C), 135.27, 135.34 (2'C), 149.68-149.76 (6C and *ipso*-Ph), 155.28 (4C), 158.97 (2C), 173.12, 173.23 (C=O); *m/z* (FAB) 570.2610 (MH⁺, C₂₇H₃₇N₇O₅P requires 570.2594).

20

Phenyl(methoxy-L-prolinyl)phosphorochloridate



30

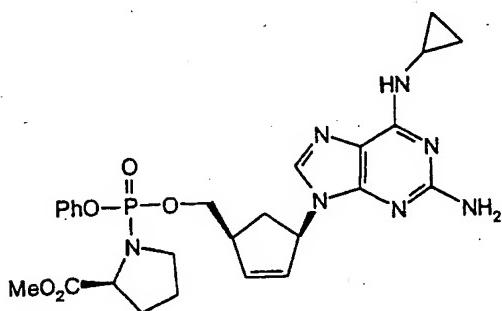
Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.54 ml, 3.6 mmol), dry triethylamine (1.0 ml, 7.2 mmol), L-proline methyl ester hydrochloride salt

(0.6 g, 3.6 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (1.24 g, >100 %).

δ_{P} (CDCl_3 , 121 MHz) 9.02, 9.22

- 5 The product was redissolved in dry THF (5 ml) and used as a 0.248 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
 O-[phenyl(methoxy-L-prolinyl)phosphate [Cf 1719]



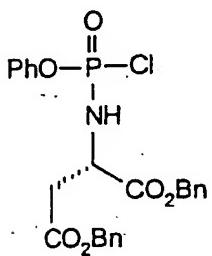
Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), $^t\text{BuMgCl}$ (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(methoxy-L-prolinyl) phosphorochloridate 17a (2.6 ml of 0.248 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl_3) showed the reaction to be complete after 20 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl_3 (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.168 g, 0.3 mmol, 44 %).

δ_P (CDCl_3 , 121 MHz) 2.83, 2.90; δ_H (CDCl_3 , 300 MHz) 0.65 (m, 2H, $\text{CH}_2\text{-cPr}$), 0.90 (m, 2H, $\text{CH}_2\text{-cPr}$), 1.92 (m, 5H, $\text{CH}_2\text{CH}_2\text{-pro}$ and 6'H_a), 2.83 (m, 1H, 6'H_b), 3.04 (m, 1H, $\text{CH}\text{-cPr}$), 3.17 (m, 1H, 4'H), 3.45 (m, 2H, N- $\text{CH}_2\text{-pro}$), 3.70 (d, 3H, OCH_3), 4.13 (m, 1H, $\text{CH}\text{-pro}$), 4.30 (m, 2H, 5'H), 4.87 (bs, 2H, NH_2), 5.56 (m, 1H, 1'H), 5.73 (bs, 1H, $\text{NH}\text{-cPr}$), 5.91 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 7.27 (m, 5H, ArH), 7.55 (d, 1H, 8H); δ_C (CDCl_3 , 75 MHz) 6.42 ($\text{CH}_2\text{-cPr}$), 22.62 ($\text{CH}\text{-cPr}$), 23.91, 24.02 ($\text{CH}_2\text{-pro}$), 30.38, 30.49 ($\text{CH}_2\text{-pro}$), 33.54 (6'C), 44.61, 44.72 (4'C), 46.89 (N- CH_2), 51.07, 51.19 (OCH_3), 57.71, 57.80 (1'C),

58.84, 58.92 (CH-pro), 67.67, 67.75 (5'C), 113.87 (5C), 118.90-119.22 (*o*-Ph), 123.64, 123.73 (*p*-Ph), 128.55, 128.59 (*m*-Ph), 130.00 (3'C), 134.46 (8C), 135.42, 135.63 (2'C), 149.81, 149.90 (6C and *ipso*-Ph), 155.20 (4C), 158.87 (2C), 172.72, 173.23 (C=O); *m/z* (FAB) 554.2283 (MH^+ , $C_{26}H_{33}N_7O_5P$ requires 554.2281).

5

Phenyl(dibenzylxy-L-aspartinyl)phosphorochloridate

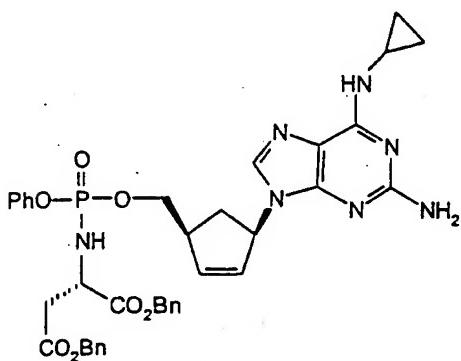


Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-aspartate dibenzyl ester *p*-toluene sulfonate salt (1.46 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was 20 obtained as a clear, yellow oil (0.8024 g, 55 %).

δ_P (CDCl₃, 121 MHz) 9.43, 9.58

The product was redissolved in dry THF (5 ml) and used as a 0.16 g/ml solution.

25 (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(dibenzylxy-L-aspartinyl)phosphate [Cf 1720]



- Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.157 g, 0.55 mmol), 'BuMgCl (1.0 M in THF: 1.1 ml, 1.1 mmol), phenyl(dibenzylxy-l-aspartinyl) phosphorochloridate 18a (5.0 ml of 0.16 g/ml solution, 1.6 mmol) and dry THF (10 ml).
- 5 TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl₃ (3:97) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.284 g, 0.4 mmol, 70 %).
- δ_P (CDCl₃, 121 MHz) 3.68, 4.24; δ_H (CDCl₃, 300 MHz) 0.63 (m, 2H, CH₂-cPr), 0.85 (m, 10 2H, CH₂-cPr), 1.63 (m, 1H, 6'H_a), 2.71 (m, 1H, 6'H_b), 3.06 (m, 2H, CH-cPr and 4'H), 4.14 (m, 2H, CH-asp, NH-asp), 4.34 (m, 2H, 5'H), 4.98 (bs, 2H, NH₂), 5.06 (d, 2H, OCH₂Ph), 5.13 (d, 2H, OCH₂Ph), 5.53 (m, 1H, 1'H), 5.88 (m, 2H, NH-cPr and 3'H), 6.01 (m, 1H, 2'H), 7.25 (m, 15H, ArH), 7.49 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 22.64 (CH-cPr), 33.40 (6'C), 37.44, 37.60 (CH₂-asp), 44.50, 44.57 (4'C), 50.20, 50.33 (CH-asp), 15 57.79 (1'C), 65.77 (OCH₂Ph), 66.65 (OCH₂Ph), 67.86, 68.00 (5'C), 113.85 (5C), 119.09-119.34 (o-Ph), 123.92 (p-Ph), 127.34-127.55 (m-Ph and m/p-Bn), 128.61 (o-Bn), 130.06 (3'C), 134.00 (ipso-Bn), 134.03 (ipso-Bn), 134.61 (8C), 135.23, 135.27 (2'C), 149.47-149.91 (6C and ipso-Ph), 155.28 (4C), 158.95 (2C), 169.22, 169.43, 170.00, 170.29 (C=O).
- 20
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl (2-methylpropyl)oxyalaninyl phosphate) CF1672
- This was prepared by Standard Procedure 4. 70% yield.
- δ_P 3.87, 3.91.
- 25 δ_H 0.64 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 0.92 (8H, m, CH_aH_b, CH_aH_b, cyclopropyl, CH(CH₃)₂), 1.42 (3H, m, CH₃ alaninyl), 1.71 (1H, m, 6'-H_aH_b), 1.92 (1H, m, CH(CH₃)₂), 2.81 (1H, m, 6'-H_aH_b), 3.03 (1H, m, CH cyclopropyl), 3.19 (1H, m, 4'-H), 3.87 (3H, m, CH alaninyl, CH₂CH(CH₃)₂), 4.09 (1H, m, NH alaninyl), 4.20 (2H, m, 5'-H), 4.91 (2H, br s, NH₂), 5.53 (1H, br m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.92 (1H, m, 3'-H), 6.12 (NH₂), 30 (1H, m, 2'-H), 7.31 (5H, m, Ph-H), 7.48 (1H, br d, 8H)
- δ_C 5.45 (CH₂-cyclopropyl x 2), 17.01 (CH(CH₃)₂), 19.23, 19.29 (Me alaninyl), 21.74 (CH-cyclopropyl), 25.72 (CH(CH₃)₂), 32.58, 32.64 (6'-C), 43.66, 43.76 (4'-C), 48.35 (CH alaninyl), 56.90 (1'-C), 66.88, 66.96, 67.03 (5'-C), 69.57, 69.60 (CH₂CH(CH₃)₂), 118.17,

118.20, 118.24, 118.27 (*o*-Ph, 5-C), 122.94 (*p*-Ph), 127.70 (*m*-Ph), 129.19, 129.24 (3'-C), 134.35, 134.45 (8-C, 2'-C), 148.81, 148.72 (*i*-Ph), 149.62, 149.76 (6-C), 154.34 (4-C), 158.91, 158.96 (2-C), 171.68, 171.58 (C(O) alaninyl).

MS m/e 570.2505 (M^+ , $C_{27}H_{36}N_7O_5P$ requires 570.2515).

- 5 HPLC t_R 33.11 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

**(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl (2,2-dimethylpropyl)oxylalaninyl phosphate) CF1673**

- 10 This was prepared by Standard Procedure 4. 94% yield.

δ_p 3.88, 3.94.

δ_H 0.61 (2H, m, CH_aH_b , CH_aH_b cyclopropyl), 0.85 (2H, br m, CH_aH_b , CH_aH_b cyclopropyl), 0.91 (9H, s, $C(CH_3)_3$), 1.41 (3H, m, CH_3 alaninyl), 1.70 (1H, m, 6'- H_aH_b), 2.78 (1H, m, 6'- H_aH_b), 3.03 (1H, m, CH cyclopropyl), 3.18 (1H, m, 4'-H), 3.81 (3H, m, CH

- 15 alaninyl, $CH_2CH(CH_3)_2$, 4.09 (1H, m, NH alaninyl), 4.20 (2H, m, 5'-H), 4.97 (2H, br s, NH₂), 5.52 (1H, br m, 1'-H), 5.86 (1H, br s, NH-cyclopropyl, 3'-H), 6.08 (1H, m, 2'-H), 7.25 (5H, m, Ph-H), 7.48 (1H, br d, 8H).

δ_C 7.89 (CH_2 -cyclopropyl x 2), 21.74, 21.77 (Me alaninyl), 26.81 ($C(CH_3)_3$), 24.21 (CH-cyclopropyl), 31.90 ($C(CH_3)_3$), 35.06 (6'-C), 46.10, 46.20 (4'-C), 50.79, 50.83 (CH

- 20 alaninyl), 59.42 (1'-C), 66.35 (5'-C), 69.34, 69.41, 69.49 ($CH_2C(CH_3)_3$), 116.41 (5-C), 120.62, 120.66, 120.68, 120.72 (*o*-Ph), 125.39 (*p*-Ph), 130.15 (*m*-Ph), 131.61, 131.65 (3'-C), 136.82, 136.90 (8-C, 2'-C), 151.16, 151.25 (6-C, *i*-Ph), 156.78 (4-C), 158.91, 160.44 (2-C), 174.09, 174.20 (C(O) alaninyl).

ES+ m/e 584.2640 (MH^+ , $C_{28}H_{39}N_7O_5P$ requires 584.2672).

- 25 HPLC t_R 34.97 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

**(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl (3-methylbutyl)oxylalaninyl phosphate) CF1674**

- 30 This was prepared by Standard Procedure 4. 47% yield.

δ_p 3.87, 3.89:

δ_H 0.57 (2H, m, CH_aH_b , CH_aH_b cyclopropyl), 0.80 (8H, m, CH_aH_b , CH_aH_b cyclopropyl, $CH(CH_3)_2$), 1.30 (3H, m, CH_3 alaninyl), 1.42 (2H, m, OCH_2CH_2), 1.62 (2H, m, 6'- H_aH_b ,

- $\text{CH}(\text{CH}_3)_2$, 2.70 (1H, m, 6'- H_aH_b), 2.92 (1H, br s, CH cyclopropyl), 3.07 (1H, m, 4'-H), 3.88 (3H, m, CH alaninyl, OCH_2CH_2), 4.07 (3H, m, NH alaninyl, 5'-H), 4.91 (2H, br s, NH_2), 5.48 (1H, br m, 1'-H), 5.83 (2H, br s, NH-cyclopropyl, 3'-H), 6.03 (1H, m, 2'-H), 7.18 (5H, m, Ph-H), 7.42 (1H, br d, 8H).
- 5 δ_{C} 7.81 (CH_2 -cyclopropyl x 2), 21.49, 21.56 (Me alaninyl), 22.79, 22.83 ($\text{CH}(\text{CH}_3)_2$), 24.10 ($\text{CH}(\text{CH}_3)_2$), 25.38 (CH-cyclopropyl), 34.91, 34.99 (OCH_2CH_2), 37.54 (6'-C), 46.01, 46.11 (4'-C), 50.70 (CH alaninyl), 59.25, 59.29 (1'-C), 64.63, 64.66 (OCH_2CH_2), 69.22; 69.30, 69.38 (5'-C), 116.17 (5-C), 120.53, 120.55, 120.59, 120.61 (*o*-Ph), 125.28 (*p*-Ph), 130.05 (*m*-Ph), 131.54, 131.60 (3'-C), 135.96 (8-C), 136.70, 136.81 (2'-C), 151.09, 151.17
- 10 (6-C, *i*-Ph), 156.68 (4-C), 160.34 (2-C), 173.94, 174.05 (C(O) alaninyl).
 ES+ m/e 584.2664 (MH^+ , $\text{C}_{28}\text{H}_{39}\text{N}_7\text{O}_5\text{P}$ requires 584.2672).
 HPLC t_{R} 38.51 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).
- 15 (**1S,4R**)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
 O-(phenyl (cycloheptanyl)oxyalaninyl phosphate) CF1752
 This was prepared by Standard Procedure 4. 41% yield.
 δ_{P} 3.96, 3.98.
 δ_{H} 0.68 (2H, m, CH_aH_b , CH_aH_b cyclopropyl), 0.99 (2H, m, CH_aH_b , CH_aH_b cyclopropyl), 1.36 (5H, m, CH_3 alaninyl, 5"- H_aH_b , 6"- H_aH_b), 1.80 (11H, m, 6'- H_aH_b , 2"-H, 3"-H, 4"-H, 7"-H, 5"- H_aH_b , 6"- H_aH_b), 2.80 (1H, m, 6'- H_aH_b), 3.12 (1H, br s, CH cyclopropyl), 3.22 (1H, m, 4'-H), 3.97 (2H, m, CH alaninyl, NH alaninyl), 4.20 (2H, m, 5'-H), 4.95 (1H, m, O-CH), 5.18 (2H, br s, NH_2), 5.57 (1H, br m, 1'-H), 5.90 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 6.25 (1H, br s, NH cyclopropyl), 7.25 (5H, m, Ph-H), 7.51 (1H, br d, 8H).
- 20 δ_{C} 15.08 (CH_2 -cyclopropyl x 2), 28.76, 28.82 (Me alaninyl), 30.40, 30.44 (3"-C, 6"-C), 24.10 ($\text{CH}(\text{CH}_3)_2$), 31.57 (CH-cyclopropyl), 35.87 (4"-C, 5"-C), 41.26, 41.29, 41.31, 41.36 (6'-C), 42.24 (2"-C, 7"-C), 53.32, 53.42 (4'-C), 58.08 (CH alaninyl), 61.15 (1'-C), 66.62 (5'-C), 116.17 (5-C), 127.81, 127.85, 127.88, 127.91 (*o*-Ph), 132.54 (*p*-Ph), 137.32, 137.49 (*m*-Ph), 138.75 (3'-C), 143.21 (8-C), 144.13, 144.22 (2'-C), 158.40, 158.49 (6-C, *i*-Ph), 164.42 (4-C), 167.41 (2-C), 180.47, 180.51, 180.59 (C(O) alaninyl).
 ES+ m/e 632.2719 ($\text{M}[\text{Na}]^+$, $\text{C}_{30}\text{H}_{40}\text{N}_7\text{O}_5\text{NaP}$ requires 632.2726).
 HPLC t_{R} 41.92 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-(phenyl diethoxyaspartyl phosphate) CF1714**

This was prepared by Standard Procedure 4. 54% yield.

5 δ_P 3.76, 4.19.

- δ_H 0.62 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 0.88 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 1.25 (6H, m, CH₃-CH₂-O aspartyl x 2), 1.68 (1H, m, 6'-H_aH_b), 2.75 (2H, m, -(CO)-CH_aH_b aspartyl, 6'-H_aH_b), 2.97 (2H, m, CH cyclopropyl, -(CO)-CH_aH_b aspartyl), 3.16 (1H, m, 4'-H), 4.15 (8H, m, CH aspartyl, CH₂-O aspartyl x 2, NH aspartyl, 5'-H), 4.90 (2H, br s, 10 NH₂), 5.52 (1H, br m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.90 (1H, m, 3'-H), 6.08 (1H, m, 2'-H), 7.21 (5H, m, Ph-H), 7.48 (1H, br d, 8H).
- δ_C 8.65 (CH₂-cyclopropyl x 2), 15.31 (CH₃-CH₂-O aspartyl x 2), 24.92 (CH-cyclopropyl), 35.72 ((CO)-CH₂ aspartyl), 39.74, 39.91 (6'-C), 46.82, 46.90 (4'-C), 52.41, 52.47 (CH aspartyl), 60.11 (1'-C), 62.22 (CH₃-CH₂-O(CO)CH₂ aspartyl), 63.15 (CH₃-CH₂-O(CO)CH 15 aspartyl), 70.14, 70.27, 70.35 (5'-C), 116.12 (5-C), 121.33, 121.40, 121.49, 121.55 (*o*-Ph), 126.15 (*p*-Ph), 130.86 (*m*-Ph), 132.36 (3'-C), 136.90 (8-C), 137.54 (2'-C), 151.81, 151.85 (6-C, *i*-Ph), 157.39 (4-C), 161.01 (2-C), 171.67, 171.81 (C(O)CH₂ aspartyl), 172.38, 172.48, 172.52, 172.62 (C(O) aspartyl).
- ES+ m/e 614.2393 (MH⁺, C₂₈H₃₇N₇O₇P requires 614.2492).
- 20 HPLC t_R 30.37 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-(phenyl methoxymethionyl phosphate) CF1715**

25 This was prepared by Standard Procedure 4. 49% yield.

δ_P 3.90, 4.03.

- δ_H 0.61 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 0.86 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 1.71 (1H, m, CH-CH_aCH_b methioninyl), 1.90 (1H, m, CH-CH_aCH_b methioninyl), 2.01 (3H, d, CH₃-S-), 2.30 (1H, m, 6'-H_aH_b), 2.47 (2H, m, 5'-CH₂), 2.78 (1H, m, 6'-H_aH_b), 2.97 (1H, br m, CH cyclopropyl), 3.14 (1H, m, 4'-H), 3.70 (3H, d, CH₃-O-), 3.80 (1H, m, CH methioninyl) 4.17 (3H, m, NH methioninyl, 5'-H), 4.89 (2H, br s, NH₂), 5.49 (1H, m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.90 (1H, m, 3'-H), 6.08 (1H, m, 2'-H), 7.24 (5H, m, Ph-H), 7.43 (1H, br d, 8H).

δ_C 6.52 (CH₂-cyclopropyl x 2), 14.42, 14.47 (CH₃-S-), 22.81 (CH-cyclopropyl), 28.63, 28.78 (S-CH₂), 32.62, 32.73, 32.81 (CH-CH₂- methioninyl), 33.65 (6'-C), 44.73, 44.83 (4'-C), 51.67 (CH methioninyl), 57.99 (1'-C), 68.13, 68.20, 68.27 (5'-C), 114.03 (5-C), 119.15, 119.22, 119.24, 119.30 (*o*-Ph), 124.05, 124.10 (*p*-Ph), 128.80 (*m*-Ph), 130.26, 130.30 (3'-C), 134.72 (8-C), 135.42, 135.47 (2'-C), 149.76, 149.80, 149.84, 149.89 (*i*-Ph), 150.08 (6-C), 155.38 (4-C), 159.06 (2-C), 172.25, 172.28, 172.32, 172.36 (C(O)).

ES+ m/e 588.2053 (MH⁺, C₂₆H₃₄N₇O₅PS requires 588.2080).
HPLC *t*_R 29.64 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

10

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl methoxytryptophanyl phosphate) CF1750**

This was prepared by Standard Procedure 4. 70% yield.

δ_P 3.88, 4.01.

δ_H 0.68 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 0.92 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 1.53 (1H, m, 6'-H_aH_b), 2.68 (1H, m, 6'-H_aH_b), 2.99 (2H, br m, CH cyclopropyl, 4'-H), 3.22 (2H, m, CH₂-Trp), 3.66 (3H, d, CH₃-O-), 3.93 (3H, m, NH Trp, 5'-H), 4.35 (1H, m, CH Trp), 4.94 (2H, br s, NH₂), 5.49 (1H, m, 1'-H), 5.87 (2H, m, NH-cyclopropyl, 3'-H), 5.97 (1H, m, 2'-H), 7.01 (1H, m, 6"-H), 7.26 (7H, m, Ph-H, 4"-H, 5"-H), 7.46 (1H, m, 7"-H), 7.52 (1H, m, 2"-H), 8.63 (1H, br d, 8H).

δ_C 7.81 (CH₂-cyclopropyl x 2), 24.10 (CH-cyclopropyl), 34.86, 34.91 (6'-C), 45.81, 45.90, 46.00 (4'-C), 52.97 (CH Trp), 59.24, 59.29 (1'-C), 69.14, 69.20 (5'-C), 109.86, 110.11 (3"-C), 111.72 (7"-C), 118.91 (5-C), 119.95, 120.04 (4"-C, 5"-C), 120.40, 120.47, 120.57, 120.63 (*o*-Ph), 122.49, 122.56 (6"-H), 123.70 (2"-C), 125.23, 125.29 (*p*-Ph), 127.79, 127.98 (9"-C), 130.04 (*m*-Ph), 131.27 (3'-C), 136.08 (8-C), 136.50, 136.55, 136.76, 136.87 (2'-C, 8"-C), 151.05, 151.14, 151.17, 151.26 (*i*-Ph, 6-C), 156.68 (4-C), 160.35 (2-C), 173.58, 173.66 (C(O)).

ES+ m/e 643.2432 (MH⁺, C₃₂H₃₆N₈O₅P requires 643.2546).
HPLC *t*_R 31.46 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl methoxyisoleucinyl phosphate) CF1751**

This was prepared by Standard Procedure 4. 60% yield.

δ_P 4.48, 4.54.

- δ_H 0.68 (2H, m, CH_2H_b , CH_2H_b cyclopropyl), 0.91 (8H, m, CH_2H_b , CH_2H_b cyclopropyl,
 5 $CH_3 \times 2$ isoleucinyl), 1.15 (1H, m, CH_2CH_b isoleucinyl), 1.45 (1H, m, CH_2CH_b isoleucinyl), 1.75 (2H, m, 6'- H_bH_b , CH_2CH), 2.83 (1H, m, 6'- H_bH_b), 3.05 (1H, br m, CH cyclopropyl), 3.19 (1H, m, 4'-H), 3.62 (1H, m, NH isoleucinyl), 3.71 (3H, d, CH_3-O-), 3.88 (1H, m, CH isoleucinyl), 4.21 (2H, m, 5'-H), 4.91 (2H, br s, NH_2), 5.55 (1H, m, 1'-H), 5.81 (1H, br s, NH-cyclopropyl), 5.93 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 7.28 (5H, m, Ph-H), 7.52 (1H, br d, 8H).
- 10 δ_C 7.82 (CH_2 -cyclopropyl x 2), 11.89 (CH_3CH_2), 15.72 (CH_3CH), 24.08 (CH-cyclopropyl), 25.04, 25.13. (CH_3CH_2), 34.99 (6'-C), 39.49, 39.56, 39.64 (CH_2CH), 46.04, 46.14 (4'-C), 52.46, 52.50 (CH isoleucinyl), 59.24, 59.44, 59.54 (1'-C), 69.34 (5'-C), 116.12 (5-C), 120.47, 120.53, 120.58 (*o*-Ph), 125.27 (*p*-Ph), 130.03 (*m*-Ph), 131.50, 131.57 (3'-C), 136.04 (8-C), 136.84, 136.74 (2'-C), 151.10, 151.18, 151.27 (*i*-Ph; 6-C), 156.69 (4-C), 161.06, 161.09, 161.35, 161.41 (2-C), 173.48, 173.53 (C(O)).

ES+ m/e 570.2496 (MH^+ , $C_{27}H_{37}N_7O_5P$ requires 570.2594).

HPLC t_R 32.83, 33.14 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

20 (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
 O-(phenyl dimethoxyglutamyl phosphate) CF1749

This was prepared by Standard Procedure 4. 38% yield.

δ_P 3.99.

- δ_H 0.68 (2H, m, CH_2H_b , CH_2H_b cyclopropyl), 0.91 (2H, m, CH_2H_b , CH_2H_b cyclopropyl),
 25 1.73 (1H, m, 6'- H_bH_b), 2.12 (1H, m, C(O) $CH_2CH_2H_b$), 2.38 (2H, m, C(O) CH_2), 2.82 (1H, m, 6'- H_bH_b), 3.05 (1H, m, CH cyclopropyl), 3.18 (1H, m, 4'-H), 3.68 (3H, s, MeOC(O) CH_2), 3.72 (3H, s, MeOC(O)CH), 3.85 (1H, m, NH glutyl), 4.10 (1H, m, CH glutyl), 4.21 (2H, m, 5'-H), 4.95 (2H, br s, NH_2), 5.57 (1H, br m, 1'-H), 5.88 (1H, br s, NH-cyclopropyl), 5.95 (1H, m, 3'-H), 6.10 (1H, m, 2'-H), 7.25 (5H, m, Ph-H), 7.54 (1H, br s, 30 8H).
- δ_C 7.82 (CH_2 -cyclopropyl x 2), 24.12 (CH-cyclopropyl), 29.66, 29.73, 29.88 (C(O) CH_2CH_2), C(O) CH_2CH_2), 34.91 (6'-C), 46.02, 46.12 (4'-C), 52.19 ($CH_3OC(O)CH_2CH_2$), 54.17, 54.28 ($CH_3OC(O)CH_2$), 54.17 (CH glutyl), 59.31 (1'-C),

- 69.50 (5'-C), 115.42 (5-C), 120.48, 120.51, 120.55, 120.58 (*o*-Ph), 125.39 (*p*-Ph), 130.09, 130.22 (*m*-Ph), 131.55, 131.60 (3'-C), 136.13 (8-C), 1136.68, 136.77 (2'-C), 150.98, 151.05, 151.13 (6-C), 151.76 (*i*-Ph), 156.65 (4-C), 160.99, 161.02, 161.08, 161.12 (2-C), 173.33, 173.43 (C(O) x 2 glutyl).
- 5 ES+ m/e 600.2216 (MH^+ , $C_{27}H_{35}N_7O_7P$ requires 600.2335).
 HPLC t_R 27.25 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
 O-(phenyl (methoxy- α -ethylglycyl phosphate) CF1783**
- 10 This was prepared by Standard Procedure 4. 44% yield.
- δ_P 4.10.
 δ_H 0.59 (2H, m, CH_2H_b , CH_2H_b' cyclopropyl), 0.83 (5H, br m, CH_2H_b , CH_2H_b' cyclopropyl, CH_3-CH_2), 1.68 (3H, m, CH_3-CH_2 , 6'- H_a), 2.69 (1H, m, 6'- H_aH_b), 2.91 (1H, m, 4'-H), 3.06 (1H, m, CH cyclopropyl), 3.58 (3H, d, J 3.0, MeO), 3.90 (2H, m, NH glycyl, CH glycyl), 4.07 (2H, m, 5'-H), 5.02 (2H, br s, NH₂), 5.42 (1H, m, 1'-H), 5.75 (1H, m, 3'-H), 5.98 (1H, m, 2'-H), 6.03 (1H, m, NH cyclopropyl), 7.18 (5H, m, Ph-H), 7.41 (1H, br d, 8H).
 δ_C 7.76 (CH_2 -cyclopropyl x 2), 9.68, 9.76 (CH_3CH_2), 24.12 (CH-cyclopropyl), 28.05 (20 CH_3CH_2), 35.01 (6'-C), 46.02, 46.13 (4'-C), 52.70, 52.73 (CH_3O), 56.02 (1'-C), 59.25 (CH-ala), 69.38 (5'-C), 116.10 (5-C), 120.48, 120.50, 120.55, 120.57 (*o*-Ph), 125.27 (*p*-Ph), 130.04 (*m*-Ph), 131.51 (3'-C), 135.86 (8-C), 136.86 (2'-C), 151.08, 151.13, 151.22 (6-C, *i*-Ph), 156.67 (4-C), 160.40 (2-C), 173.84, 173.87, 173.92 (C(O) alanyl).
 ES+ m/e 564.2094 ($M[Na]^+$, $C_{25}H_{32}N_7O_5NaP$ requires 564.2100).
 25 HPLC t_R 16.82, 16.84 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
 O-(phenyl (methoxy- α -phenyl(RS)glycyl phosphate) CF1784**
- 30 This was prepared by Standard Procedure 4. 46% yield.
- δ_P 3.18, 3.28, 3.42, 4.29.
 Proton and Carbon NMR gave complex spectra, consistent with the racemised product.
 ES+ m/e 612.2086 ($M[Na]^+$, $C_{29}H_{32}N_7O_5NaP$ requires 612.2100).

HPLC t_R 17.63, 18.50 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)). (1:1.08 racemisation by HPLC)

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

5 **O-(phenyl (methoxy- α -butylglycyl phosphate) CF1786**

This was prepared by Standard Procedure 4. 51% yield.

δ_P 4.10, 4.16.

δ_H 0.51 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 0.72 (5H, br m, CH_aH_b, CH_aH_b cyclopropyl, CH₃-CH₂), 1.18 (4H, m, CH₃-CH₂-CH₂-), 1.54 (3H, m, CH₂-CH₂-O, 6'-H_aH_b), 2.73 (1H, m, 6'-H_aH_b), 2.93 (1H, m, 4'-H), 3.09 (1H, m, CH cyclopropyl), 3.52 (1H, m, CH glycyl), 3.62 (3H, s, MeO), 3.87 (1H, m, NH glycyl), 4.12 (2H, m, 5'-H), 4.75 (2H, br s, NH₂), 5.45 (1H, m, 1'-H), 5.79 (2H, br s, NH-cyclopropyl, 3'-H), 6.00 (1H, m, 2'-H), 7.20 (5H, m, Ph-H), 7.42 (1H, br d, 8H).

δ_C 7.76 (CH₂-cyclopropyl x 2), 14.23 (CH₃CH₂), 22.56 (CH₃CH₂), 24.14 (CH-cyclopropyl), 27.43, 27.50 (CH₃CH₂CH₂), 34.50, 34.58 (CH₂CH₂O), 35.01 (6'-C), 46.02, 46.12 (4'-C), 52.66, 52.68 (CH₃O), 54.87, 54.94 (1'-C), 59.20 (CH-ala), 69.30, 69.37 (5'-C), 115.18 (5-C), 120.29, 120.42, 120.50, 120.57 (*o*-Ph), 125.21 (*p*-Ph), 130.00 (*m*-Ph), 131.51, 131.54 (3'-C), 135.86 (8-C), 136.71, 136.76 (2'-C), 151.12, 151.16, 151.20, 151.25 (6-C, *i*-Ph), 156.73 (4-C), 160.49, 160.96 (2-C), 174.19, 174.26 (C(O) glycyl).

20 ES+ m/e 592.2428 [M+Na]⁺, C₂₇H₃₆N₇O₅NaP requires 592.2413).

HPLC t_R 18.34; 18.41, min and 16.64 min (6:1) (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

* Note: compound isolated as 6:1 (S:R) stereoisomeric mixture at the amino acid residue α -carbon. Additional resonances in the ³¹P NMR spectra are noted at 4.35 and 5.18, corresponding to the minor configuration (R) amino acid residue containing diastereoisomers.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-(phenyl (methoxy- α -propylglycyl phosphate) CF1785

30 This was prepared by Standard Procedure 4. 50% yield.

δ_P 4.14, 4.21.

δ_H 0.62 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 0.86 (5H, br m, CH_aH_b, CH_aH_b cyclopropyl, CH₃-CH₂), 1.32 (2H, m, CH₃-CH₂-), 1.63 (3H, m, CH₃-CH₂, 6'-H_aH_b), 2.79

(1H, m, 6'-H_aH_b), 3.03 (1H, m, 4'-H), 3.18 (1H, m, CH cyclopropyl), 3.71 (3H, d, J 3.0, MeO), 3.97 (1H, m, CH glycinal), 4.15 (3H, m, 5'-H, NH glycinal), 5.09 (2H, br s, NH₂), 5.55 (1H, m, 1'-H), 5.90 (1H, m, 3'-H), 6.08 (2H, m, 2'-H, NH cyclopropyl), 7.23 (5H, m, Ph-H), 7.52 (1H, br d, 8H).

- 5 δ_C 7.55 (CH₂-cyclopropyl x 2), 13.98 (CH₃CH₂), 18.62, 18.70 (CH₃CH₂), 24.15 (CH-cyclopropyl), 35.00 (6'-C), 36.89, 36.96 (CH₂CH₂O), 46.02, 46.12 (4'-C), 52.68 (CH₃O), 54.70, 54.77 (1'-C), 59.21 (CH-alan), 69.31, 69.38 (5'-C), 115.24 (5-C), 120.45, 120.51, 120.57 (o-Ph), 125.22 (p-Ph), 130.01 (m-Ph), 131.54 (3'-C), 135.89 (8-C), 136.72, 136.78 (2'-C), 151.11, 151.16, 151.20, 151.25 (6-C, i-Ph), 156.72 (4-C), 160.45, 160.95 (2-C), 10 174.18, 174.25 (C(O) alaninyl).

ES+ m/e 578.2259 [M+Na]⁺, C₂₆H₃₄N₇O₅NaP requires 578.2257).

HPLC t_R 17.57 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

- 15 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((p-(2'',2''-dimethoxypropionic acid methyl ester)-phenyl)methoxyalaninyl phosphate) CF1671

This was prepared by Standard Procedure 4. 24 % yield.

δ_P 3.72, 3.84.

- 20 δ_H 0.56 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 0.79 (2H, m, CH_aH_b, CH_aH_b cyclopropyl), 1.30 (3H, m, CH₃ alaninyl), 1.63 (1H, m, 6'-H_aH_b), 2.70 (1H, m, 6'-H_aH_b), 2.95 (1H, br s, 4'-H), 3.07 (3H, m, CH cyclopropyl, Ph-CH₂-), 3.26 (6H, s, (OMe)₂), 3.52 (3H, s, C(OMe)₂COOMe), 3.61 (3H, s, COOMe alaninyl), 3.84 - 4.08 (4H, m, CH alaninyl, NH alaninyl, 5'-H), 4.99 (2H, br s, NH₂), 5.46 (1H, br m, 1'-H), 5.81 (1H, br s, 3'-H), 6.02 (2H, 25 m, 3'-H, NH-cyclopropyl), 6.02 (1H, m, 2'-H), 7.02 (4H, m, Ph-H), 7.45 (1H, br d, 8H).

- δ_C 7.77 (CH₂-cyclopropyl x 2), 21.37 (Me alaninyl), 24.01 (CH-cyclopropyl), 34.89 (6'-C), 39.55 (Ph-CH₂), 45.97, 46.09 (4'-C), 50.53 ((MeO)₂, CH₃OO alaninyl), 52.65 (C(OMe)₂COOMe), 59.28 (1'-C), 69.29 (5'-C), 103.27 (C(OMe)₂), 120.31, 120.38 (o-Ph), 122.94 (p-Ph), 131.35 (m-Ph), 131.39 (3'-C), 136.79 (8-C, 2'-C), 150.14, 150.05 (i-Ph, 6-C), 152.12 (4-C), 160.24 (2-C), 169.08 (C(OMe)₂COOMe), 174.36, 174.46 (C(O) alaninyl).

ES+ m/e 696.2531 ([M]⁺, C₃₀H₄₀N₇O₉NaP requires 696.2523).

HPLC t_R 29.02 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

5 **O-((p-methoxyphenyl)methoxylaninyl phosphate) CF1815**

This was prepared by Standard Procedure 4. 23% yield.

δ_P 4.23, 4.28.

δ_H 0.72 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 1.0 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl),

1.48 (3H, m, CH₃ alaninyl), 1.82 (1H, m, 6'-H_aH_b), 2.80 (1H, m, 6'-H_aH_b), 3.11 (1H, br s,

10 4'-H), 3.25 (1H, m, CH cyclopropyl), 3.67 (1H, m, NH alaninyl), 3.77 (3H, s, COOMe alaninyl), 3.89 (3H, s, MeO-Ar), 4.14 (1H, m, CH alaninyl), 4.30 (2H, m, 5'-H), 4.94 (2H, br s, NH₂), 5.65 (1H, br m, 1'-H), 5.83 (1H, br s, NH-cyclopropyl), 6.00 (1H, m, 3'-H), 6.17 (1H, m, 2'-H), 6.92 (2H, m, m-Ar), 7.23 (2H, m, o-Ar), 7.63 (1H, s, 8H).

δ_C 7.81 (CH₂-cyclopropyl x 2), 21.46, 21.52 (Me alaninyl), 24.00 (CH-cyclopropyl), 34.96

15 (6'-C), 46.04, 46.14 (4'-C), 50.64 (CH₃OO alaninyl), 52.89 (CH-alaninyl), 56.02 (CH₃O-Ar), 59.28 (1'-C), 69.30 (5'-C), 114.98 (m-Ph, 5-C), 121.42, 121.46, 121.52 (o-Ph), 131.52, 131.56 (3'-C), 135.98, (2'-C), 136.76, 136.87 (i-Ph), 144.61 (8-C), 156.71 (4-C), 157.01 (p-Ar), 161.40, 160.99 (2-C), 174.39, 174.50 (C(O) alaninyl).

HPLC t_R 16.28 (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0%

20 CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

O-((p-propoxypyhenyl)methoxylaninyl phosphate) CF1816

This was prepared by Standard Procedure 4. 56% yield.

25 δ_P 4.33, 4.41.

δ_H 0.62 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 0.82 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl),

1.03 (3H, t, J 6.0, CH₃-CH₂), 1.39 (3H, m, CH₃ alaninyl), 1.66 (1H, m, 6'-H_aH_b), 1.80

(2H, h, J 6.0, CH₃-CH₂), 2.79 (1H, m, 6'-H_aH_b), 3.01 (1H, br s, 4'-H), 3.12 (1H, m, CH cyclopropyl), 3.72 (3H, s, COOMe alaninyl), 3.89 (2H, t, J 6.0, CH₂-O), 4.04 (2H, m, CH

30 alaninyl, NH alaninyl), 4.17 (2H, m, 5'-H), 5.10 (2H, br s, NH₂), 5.52 (1H, br m, 1'-H), 5.51 (1H, br s, NH-cyclopropyl), 5.89 (1H, m, 3'-H), 6.04 (1H, m, 2'-H), 6.81 (2H, m, m-Ar), 7.11 (2H, m, o-Ar), 7.51 (1H, s, 8H).

δ_c 7.77 (CH_2 -cyclopropyl x 2), 10.91 ($\text{CH}_3\text{-CH}_2$), 21.39, 21.46 (Me alaninyl), 22.97 ($\text{CH}_3\text{-CH}_2$), 24.14 (CH-cyclopropyl), 34.96 (6'-C), 46.02, 46.13 (4'-C), 50.57, 50.65 (CH_3OO CH_2), 52.85, 52.87 (CH-alaninyl), 53.89 (), 59.25 (1'-C), 69.16, 69.24, 69.33 (5'-C), 70.30 ($\text{CH}_2\text{-O}$), 115.24, 115.26 (5-C), 115.57 (*m*-Ph), 121.37, 121.40, 121.43, 121.46 (*o*-Ph), 131.51, 131.57 (3'-C), 135.93, (2'-C), 136.77, 136.85 (*i*-Ph), 144.47, 144.55 (8-C), 156.54, 156.73 (4-C), 160.45 (*p*-Ar), 160.91 (2-C), 174.48, 174.59 ($\text{C}(\text{O})$ alaninyl).
 5 HPLC t_R min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

10 (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)-2-cyclopentene-1-methanol
 O-[4-hydroxyacetophenone-(methoxy-L-alaninyl)]-phosphoramidate Cf 1794

This was prepared by Standard procedure 4. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (3%:97) and MeOH:EtOAc (5:95) as eluent, to give the product as a white foam (30 mg, 17 mmol, 15%).

15 δ_P 3.496.

δ_{H} 0.66 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.53 (s, 3H, CH₃-COPh), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.1 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 3.9 (m, 1H, CH₃-CH), 4.1 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.1 (m, 2H, H'2, NHcPr) 7.2 (dd, 2H, *o*-Ar), 7.5 (m, 1H, H8), 7.8 (dd,

20 2H, *p*-Ar)

δ_c 6.371 (CH₂cPr), 20 (CH-CH₃aa), 21.671 (NHCH₃), 25 (CH₃CO), 33.458 (C'6), 44.55 (C'4), 49.5 (CHaa), 51.4 (OCH₃), 57.9 (C'1), 67.9 (C'5), 113.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 150.31 (*i*-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃), 198 (CO-Ar).

25 HPLC t_r : 15.976 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min),
0% CH₃CN (35 min)).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[4n-butylphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1795**

30 The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (3%:97) and MeOH:CH₂Cl₂ (5:95) as eluent, to give the product as a white foam (15 mg, 0.025 mmol, 4 %).

δ_p 3.93-4.00.

δ_H 0.66 (m,2H,CH₂-cPr), 0.85 (m,2H,CH₂-cPr), 1.1 (m,3H, CH₃-CH₂), 1.2 (m,4H, CH₂-CH₂), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.5 (m, 2H, CH₂-Ar), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.1 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 3.9 (m, 1H, CH₃-CH), 4.1 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H,H'1), 5.85 (m, 1H, H'3), 6.1 (m, 2H, H'2,NHcPr), 7.2 5 (dd, 2H, *o*-Ar), 7.5 (m, 1H, H8), 7.8 (dd, 2H, *p*-Ar).

δ_C 6.371 (CH₂cPr), 14.345 (CH₃-CH₂), 21.49 (CH-CH₃aa), 22.66 (CH₂-CH₃), 21.671 (NHCH₃), 30.127 (CH₂-CH₂-CH₂), 33.458 (C'6), 34.047.(CH₂-Ar), 44.55 (C'4), 49.5 (CHaa), 51.4 (OCH₃), 57.9 (C'1), 67.9 (C'5), 113.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8),146.58 (*i*-Ar) 155.18 (C6), 156.342 10 (C2), 158.8 (C4), 173.004 (COOCH₃)

HPLC t_r : 19.591 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

15 **O-[phenylphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1788**

The crude residue was purified three times by column chromatography, using MeOH:CHCl₃ (3:97) and MeOH:CH₂Cl₂ (5:95) and MeOH:AcOEt (3:97) as eluent, to give the product as a yellow foam (35 mg, 0.058 mmol, 8 %).

δ_P 3.94-3.96.

20 δ_H 0.66 (m,2H,CH₂-cPr), 0.85 (m,2H,CH₂-cPr), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.25 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 4.1 (m, 1H, CH₃-CH), 4.25 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H,H'1), 5.85 (m, 1H, H'3), 6.15 (m, 2H, H'2,NHcPr), 7.35 (m, 9H, Ar), 7.6 (m, 1H, H8).

δ_C 6.371 (CH₂cPr), 21.49 (CH-CH₃aa), 21.671 (NHCH₃), 33.458 (C'6), 46.14 (C'4), 25 50.671 (CHaa), 52.9 (OCH₃), 59.9 (C'1), 65.9 (C'5), 115.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 145.25 (*i*-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃).

HPLC t_r : 19.147 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-[phenoxyphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1787**

The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (3:97) and MeOH:CH₂Cl₂ (5:95) as eluent, to give the product as a yellow foam (35 mg, 5 0.058 mmol, 8 %).

δ_P 4.212-4.184.

- δ_H 0.66 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.25 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 4.1 (m, 1H, CH₃-CH), 4.25 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.15 (10 m, 2H, H'2, NHcPr), 7.35 (m, 9H, Ar), 7.6 (m, 1H, H8).
- δ_C 6.371 (CH₂cPr), 21.49 (CH-CH₃aa), 21.671 (NHCH₃), 33.458 (C'6), 46.14 (C'4), 50.671 (CHaa), 52.9 (OCH₃), 59.9 (C'1), 65.9 (C'5), 115.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar₂), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 153.83 (*i*-Ar₂, *m*-Ar₁), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃).
- 15 HPLC t_r : 18.830 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-[phenyl methoxy- α,α -cyclopentylglycinyl] phosphate Cf 1763**

- 20 This was prepared by Standard procedure 4 in 77% yield.

- ^{31}P (CDCl₃) 3.02, 3.09
- 1H (CDCl₃) 0.56-0.61 (2H, m, CH₂ (cpro)), 0.81-0.89 (2H, m, CH₂ (cpro)), 1.58-1.78 (5H, m, CCH₂CH₂CH₂CH₂C, and H6'), 1.87-2.18 (4H, m, CCH₂CH₂CH₂CH₂C), 2.64-2.74 (1H, m, H6'), 2.83-3.09 (2H, m, CH(cpro), H4'), 3.60-3.62 (3H, s, OCH₃(ala)), 4.04-4.19 (2H, m, H5'), 5.20 (2H, bs, NH₂), 5.42-5.47 (1H, m, H1'), 5.77-5.83 (1H, m, H3'), 5.98-6.02 (1H, m, H2'), 6.20 (NH(cpro)), 7.06-7.27 (5H, m, Ar), 7.42-7.48 (1H, s, H8).
- ^{13}C (CDCl₃) 8.02 (CH₂(cpro)), 24.37, 24.41 (CCH₂CH₂CH₂CH₂C), 34.73 (C6'), 38.48, 38.68, 38.79, 38.87 (CCH₂CH₂CH₂CH₂C), 46.05, 46.15 (C4'), 52.99 (OCH₃(ala)), 59.56, 59.60 (C1'), 67.16 (C (aa), 69.28, 69.37 (C5'), 114.76 (C5), 120.46, 120.52 (*o*-Ph), 125.22 (p-Ph), 130.04 (*m*-Ph), 131.19 (C3'), 136.72 (C8), 137.13, 137.20 (C2'), 151.27, 151.31, 151.36, 151.40 (C6), 155.56 (C4), 158.95 (C2), 175.96, 176.00 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-[phenyl methoxy- α,α -cyclohexylglycinyl] phosphate Cf1764**

This was prepared by Standard procedure 4 in 15% yield.

^{31}P (CDCl_3) 2.89, 3.00

- 5 ^1H (CDCl_3) 0.74 (2H,m, CH_2 (cpro)), 1.01-1.03 (2H, m, CH_2 (cpro)), 1.29-2.23 (11H, m, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$, and $\text{H}6'$), 2.72-2.83 (1H, m, $\text{H}6'$), 3.17 (1H, bs, CH (cpro)), 3.35-3.43 (1H, m, $\text{H}4'$), 3.69-3.70 (3H, s, OCH_3 (aa)), 4.16-4.29 (2H, m, $\text{H}5'$), 5.52-5.66 (1H, m, $\text{H}1'$), 5.79 (1H, bs, NH (cpro)), 5.85-5.90 (1H, m, $\text{H}3'$), 6.08-6.10 (1H, m, $\text{H}2'$), 7.15-7.35 (5H, m, Ar), 7.37-7.63 (1H, d, H8).
- 10 ^{13}C (CDCl_3) 8.30 (CH_2 (cpro)), 21.49, 21.68, 21.84, 22.02, 22.11 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$), 25.14, 25.47, 25.72 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$), 34.37, 34.59 ($\text{C}6'$), 46.06, 46.16 ($\text{C}4'$), 52.75, 53.12 (OCH_3 (aa)), 59.95, 60.19 ($\text{C}1'$), 69.22 ($\text{C}5'$), 120.41, 120.47 (o-Ph), 125.22 (p-Ph), 130.04 (m-Ph), 130.72, 130.82 ($\text{C}3'$), 137.41 ($\text{C}8$), 137.56 ($\text{C}2'$), 151.33, 151.43 ($\text{C}6$), 175.37 (CO).

15

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl methoxy- α,α -cyclopropylglycinyl] phosphate Cf1762

This was prepared by Standard procedure 4 in 69% yield.

^{31}P (CDCl_3) 3.84

- 20 ^1H (CDCl_3) 0.68(2H,m, CH_2 (cpro)), 0.90-0.92 (2H, m, CH_2 (cpro)), 1.16-1.49 (4H, m, $\text{CCH}_2\text{CH}_2\text{C}$ (aa)), 1.66-1.72 (1H, m, $\text{H}6'$), 2.72-2.82 (1H, m, $\text{H}6'$), 3.08-3.15 (2H, m, CH (cpro), $\text{H}4'$), 3.61-3.63 (3H, d, OCH_3 (aa)), 4.24-4.26 (2H, m, $\text{H}5'$), 5.24 (2H, bs, NH_2), 5.53 (1H, bs, $\text{H}1'$), 5.87(1H, m, $\text{H}3'$), 6.07 (1H, m, $\text{H}2'$), 6.42-6.45 (1H, bs, NH (cpro)), 7.15-7.35 (5H, m, Ar), 7.56-7.61 (1H, d, H8).
- 25 ^{13}C (CDCl_3) 7.92 (CH_2 (cpro)), 18.38 (CH_2 (aa)), 35.20 ($\text{C}6'$), 52.88 (OCH_3 (aa)), 59.45 ($\text{C}1'$), 69.32 ($\text{C}5'$), 120.52 (o-Ph), 125.29 (p-Ph), 130.04 (m-Ph), 137.03 ($\text{C}2'$), 151.13 ($\text{C}6$), 160.96, 160.98 ($\text{C}2$), 174.35 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**O-[p-(methoxycarbonyl)phenyl methoxy-L-alaninyl] phosphate Cf1766**

This was prepared by Standard procedure 4 in 37% yield.

^{31}P (CDCl_3) 3.54, 3.58

¹H (CDCl₃) 0.66-0.69 (2H, m, CH₂ (cpro)), 0.88-0.94 (2H, m, CH₂ (cpro)), 1.38-1.43 (3H, t, CH₃(ala)), 1.70-1.81 (1H, m, H6'), 2.76-2.89 (1H, m, H6'), 3.07 (1H, m, CH(cpro)), 3.21 (1H, m, H4'), 3.71-3.73 (3H, d, OCH₃(ala)), 3.94 (3H, s, COOCH₃), 3.98-4.12 (1H, m, CH(ala)), 4.20-4.31 (2H, m, H5'), 5.19 (2H, bs, NH₂), 5.54-5.57 (1H, m, H1'), 5.91-5.96 (1H, m, H3'), 6.09-6.14 (1H, m, H2'), 6.21 (1H, bs, NH(cpro)), 7.27-7.32 (2H, m, ArO₂H), 7.53-7.54 (1H, d, H8), 8.02-8.06 (2H, m, COAr₂H).

¹³C (CDCl₃) 7.75 (CH₂(cpro)), 21.22, 21.29, 21.46 (CH₃(ala)), 24.16 (NHCH), 34.83 (C6'), 45.97, 46.07 (C4'), 50.59 (CH(ala)), 52.57, 59.32 (OCH₃ (ala), OCH₃(Ph)), 59.27, 59.32 (C1'), 69.43 (C5'), 115.07, 115.11 (C5), 120.28, 120.31, 120.34, 120.38 (o-Ph), 127.07 (p-Ph), 131.58, 131.66 (m-Ph), 131.88 (C3'), 135.94, 136.04 (C2'), 136.61, 136.73 (C8), 151.31 (C6), 156.52 (C2), 160.97 (C4), 171.57 (CO), 174.30, 174.39 (CO).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[p-(trifluoromethylthio)phenyl methoxy-L-alaninyl] phosphate Cf 1769**

15 This was prepared by Standard procedure 4 in 34% yield.

³¹P (CDCl₃) 3.67, 3.88

¹H (CDCl₃) 0.81 (2H, bs, CH₂ (cpro)), 1.06-1.08 (2H, m, CH₂ (cpro)), 1.50-1.54 (3H, t, CH₃(ala)), 1.83-1.93 (1H, m, H6'), 2.87-2.99 (1H, m, H6'), 3.23-3.31 (1H, m, CH(cpro)), 3.82-3.84 (3H, d, OCH₃(ala)), 4.14-4.15 (1H, m, CH(ala)), 4.32-4.40 (2H, m, H5'), 5.65 (3H, bs, H1', NH₂), 6.01-6.04 (1H, m, H3'), 6.19-6.23 (1H, m, H2'), 6.64 (1H, bs, NH(cpro)), 7.37-7.43 (2H, m, Ar), 7.67 (1H, d, H8), 7.73-7.76 (2H, m, Ar).

¹³C (CDCl₃) 8.16 (CH₂(cpro)), 21.39, 21.45 (CH₃(ala)), 34.45 (C6'), 46.09 (C4'), 50.66 (CH(ala)), 53.01 (OCH₃ (ala)), 59.87 (C1'), 69.34 (C5'), 77.47, 77.67 (CF₃S ?), 121.64, 121.69 (o-Ph), 127.07 (p-Ph), 136.99, 137.14 (C2'), 138.56 (C8), 153.36, 153.45 (C6), 160.93 (C4), 174.27 (CO).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[p-(2-methoxyvinyl)phenyl methoxy-L-alaninyl] phosphate Cf 1767**

This was prepared by Standard procedure 4 in 38% yield.

30 ³¹P (CDCl₃) 3.70, 3.74

¹H (CDCl₃) 0.58-0.61 (2H, bs, CH₂ (cpro)), 0.81-0.85 (2H, m, CH₂ (cpro)), 1.30-1.36 (3H, t, CH₃(ala)), 1.61-1.72 (1H, m, H6'), 2.33 (3H, s, CH₃CO), 2.70-2.79 (1H, m, H6'), 2.99 (1H, bs, CH(cpro)), 3.13 (1H, bs, H4'), 3.64-3.65 (3H, d, OCH₃(ala)), 3.92-4.01 (1H, m,

$\text{CH}(\text{ala})$), 4.11-4.21 (2H, m, H5'), 5.14 (3H, bs, H1', NH₂), 5.47-5.49 (1H, m, H1'), 5.82-5.87 (1H, m, H3'), 6.01-6.06 (1H, m, H2'), 6.12 (1H, bs, NH(cpro)), 6.57-6.63 (1H, dd, CH₃COCH=CH), 7.14-7.46 (6H, m, H8, Ar, CH₃COCH=CH).

- ¹³C (CDCl₃) 7.95 (CH₂(cpro)), 21.45 (CH₃(ala)), 28.02 (CH₃CO), 34.69 (C6'), 46.11 (C4'), 5 50.64 (CH(ala)), 52.99 (OCH₃ (ala)), 59.53 (C1'), 121.03, 121.10, 121.17 (o-Ph), 127.39 (p-Ph), 130.13 (CH₃COCH=CH), 131.44, 131.55 (C3'), 136.76 (C2'), 142.59 (CH₃COCH=CH), 152.72 (C6), 174.26, 174.36 (CO(ala)), 198.70 (COCH₃).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol

- 10 **O-[p-(2-phenylcarbonylvinyl)phenyl methoxy-L-alaninyl] phosphate Cf 1771**

This was prepared by Standard procedure 4 in 26% yield.

³¹P (CDCl₃) 3.75, 3.79

- ¹H (CDCl₃) 0.61-0.66 (2H,m, CH₂ (cpro)), 0.85-0.91 (2H, m, CH₂ (cpro)), 1.39-1.44 (3H, m, CH₃(ala)), 1.67-1.86 (1H, m, H6'), 2.77-2.87 (1H, m, H6'), 3.04-3.05 (1H, bs, 15 CH(cpro)), 3.19-3.21 (1H, bs, H4'), 3.72-3.73 (3H, d, OCH₃(ala)), 4.02-4.13 (1H, m, CH(ala)), 4.19-4.29 (2H, m, H5'), 5.17 (3H, bs, H1', NH₂), 5.53-5.58 (1H, m, H1'), 5.90-5.95 (1H, m, H3'), 6.09-6.15 (2H, m, H2', NH(cpro)), 7.24-8.08 (12H, m, Ar-, CH=CH, -Ar-, H8).
- ¹³C (CDCl₃) 7.85 (CH₂(cpro)), 21.35, 21.41, 21.48 (CH₃(ala)), 24.22 (CH(NH)), 34.80 (C6'), 46.01 (C4'), 50.67 (CH(ala)), 52.97 (OCH₃ (ala)), 59.37 (C1'), 69.40 (C5'), 115.07 (C5), 121.01, 121.07, 121.14 (o-Ph), 128.92, 129.06 (p-Ph), 133.27 (C3'), 136.13, 136.23 (C2'), 138.53 (C8), 152.77, 152.86 (C6), 156.31 (C2), 160.97, 160.99 (C4), 174.31, 174.41 (CO(ala)), 190.76 (CO (Ar)).

- 25 **(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol**

O-[p-(2,2-dicyanovinyl)phenyl methoxy-L-alaninyl] phosphate Cf 1768

This was prepared by Standard procedure 4 in 10% yield.

³¹P (CDCl₃) 4.54, 4.65

- 30 ¹H (CDCl₃) 0.61-0.66 (2H,m, CH₂ (cpro)), 0.85-0.91 (2H, m, CH₂ (cpro)), 1.34-1.41 (3H, m, CH₃(ala)), 1.67-1.83 (1H, m, H6'), 2.77-2.88 (1H, m, H6'), 2.95-2.97 (1H, m, CH(cpro)), 3.23 (1H, bs, H4'), 3.68-3.70 (3H, d, OCH₃(ala)), 3.99-4.03 (1H, m, CH(ala)), 4.22-4.32 (2H, m, H5'), 5.49-5.53 (1H, m, H1'), 5.99-6.03 (1H, m, H3'), 6.16-6.22 (1H, m,

H_{2'}), 6.94-6.97 (1H, dd, Ar-CH=CH), 7.36-7.41 (Ar), 7.64-7.65 (1H, d, H8), 7.92-8.16 (Ar).

¹³C (CDCl₃) 6.56 (CH₂(cpro)), 19.85 (CH₃(ala)), 23.33 (CH(cpro)), 34.23 (C6'), 46.07 (C4'), 50.47, 50.53 (OCH₃(ala)), 51.78 (CH(ala)), 59.51 (C1'), 69.19, 69.29 (C5'), 113.84, 5 114.08 (C5), 121.14, 121.21, 121.27 (o-Ph), 128.49 (p-Ph), 130.74, 130.85 (m-Ph), 132.84 (C3'), 136.01 (C2'), 136.88, 136.99 (C8), 156.47 (C2), 160.99, 161.03 (C4), 174.27 (CO).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[o-(carboxylate ethyl ester)phenyl methoxy-L-alaninyl] phosphate Cf1798**

10 This was prepared by Standard procedure 4 in 24% yield.

³¹P (CDCl₃) 4.03, 4.16

¹H (CDCl₃) 0.64-0.70 (2H,m, CH₂ (cpro)), 0.92-0.93 (2H, d, CH₂ (cpro)), 1.38-1.47 (6H, m, CH₃(ala), CH₃CH₂O), 1.73-1.83 (1H, m, H6'), 2.78-3.24 (3H, m, H6', H4', CH(cyclo)), 3.64-3.72 (3H, s, OCH₃(ala)), 4.08-4.20 (1H, m, CH(ala)), 4.23-4.45 (4H, m, H5', 15 CH₂CH₃), 5.21 (2H, bs, NH₂), 5.55-5.60 (1H, m, H1'), 5.89-5.93 (1H, m, H3'), 6.13-6.18 (1H, m, H2'), 7.23-7.61 (1H, m, H8), 7.88-7.92 (1H, d, Ar).
¹³C (CDCl₃) 7.95 (CH₂(cpro)), 14.65 (CH₃CH₂), 21.33, 21.39, 21.68, 21.74 (CH₃(ala)), 24.30 (NHCH), 34.80 (C6'), 46.04, 46.14 (C4'), 50.49 (CH(ala)), 52.74, 52.83 (OCH₃(ala)), 59.45 (C1'), 61.76, 61.82 (CH₂CH₃), 69.43, 69.51, 69.64 (C5'), 114.92 (C5), 20 122.93, 123.09, 123.60, 123.67125.26 (Ar), 131.34 (Ar), 131.77, 131.86 (C3'), 134.00 (Ar), 136.48 (C2'), 137.05 (C8), 150.20, 150.28 (C6), 155.88 (C2), 160.78, 160.86 (C4), 174.28, 174.39, 174.55, 174.65 (CO).

Example A

25 (1R, 4S)-9-[4-(hydroxymethyl)-2-cyclopenten-2-yl] guanine-5'-[phenyl-(methoxy-L-alaninyl)]-phosphate.

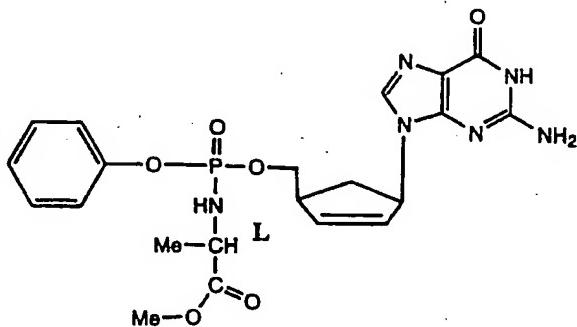
C₂₁H₂₅O₆N₆P₁, MW=488.45.

R. Vince and M. Hua, J. Med. Chem. 1990, 33, 17-21, which is hereby incorporated by reference, describes a procedure for the sysnthesis of (1R,4S)-9-{4-(hydroxymethyl)-2-cyclopenten-1-yl] guanine.

(1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl] guanine (400mg, 1.618mmol) was dried by azeotroping with anhydrous pyridine (4x10ml), kept under N₂(g), and suspended in anhydrous THF (30ml). tBuMgCl (1.0M solution in THF) (1.6ml, 1.618mmol) was added dropwise and the resulting darker suspension vigorously stirred for 10mins.

- 5 Phosphorochloridate (4.79ml, 2.43mmol) was added dropwise, and the reaction mixture stirred at room temperature for 69hrs. After this time, the suspended solid was partially in solution but a solid was still observed on the sides of the flask. More phosphorochloridate was added (4.79ml, 2.43mmol), and the reaction mixture stirred for a further 55hrs before being quenched by the addition of sat.NH₄Cl solution (0.25m). After stirring for a further
- 10 10mins, the solvent was removed under reduced pressure to give the crude product as a yellow gum which was solubilised in MeOH, dried over MgSO₄ (s), filtered and the filtrate reduced to dryness. The residue was solubilised in MeOH, silica added, and then the solvent removed to give the product preabsorbed onto silica which was loaded onto a silica column and eluted with 8% MeOH in CHCl₃. The product was further purified by gradient
- 15 elution from 5→9 MeOH in DCM on a biotage flash-40 column, and after evaporation of the appropriate fractions, the product was obtained as a white foam (70mg, 8.6%).

The compound had the formula



20

³¹P NMR (MeOH-d₄): δ 5.18, 4.86 (1:1).

¹H NMR: δ 7.67 (1H), 7.37-7.30 (2H), 7.21-7.14 (3H), 6.17-6.10 (1H), 5.97-5.94 (1H), 5.53-5.48 (1H), 4.28-4.15 (2H), 4.00-3.87 (1H), 3.66 (3H), 3.18 (1H), 2.83-2.71 (1H), 1.82-1.66 (1H), 1.36-1.29 (3H).

THIS PAGE BLANK (USPTO)



100

¹³C NMR: δ 174.4*, 158.5, 154.1, 151.7, 151.1*, 136.9*, 136.5, 130.7, 129.7, 125.0, 120.4*, 116.8, 68.9*, 59.8, 51.7, 50.5*, 46.0*, 34.2, 19.3*.

MS ES⁺ : m/z 488.86 (100%) (M)⁺, 500.04 (12%)(M+Na)⁺, 507.96 (25%)(M+K)⁺.

MS FAB: calculated m/z 489.165146, found m/z 489.164677.

5

In vitro Testing

Cells were infected with HIV-1 as previously described [Balzarini *et al.* AIDS (1991), 5
10 21-28]. Briefly, 5 x 10⁵ cells per milliliter were infected with HIV-1 or HIV-2 at 100
CCID₅₀ (50% cell culture infective dose) per milliliter of cell suspension. Then 100 μL of
the infected cell suspension was transferred to microtiter plate wells and mixed with 100
μL of the appropriate dilutions of the test compounds. After 4 days giant cell formation
was recorded microscopically in the HIV-infected cell cultures [CEM]. The 50% effective
15 concentration (EC₅₀) and 50% cytoxic concentration (CC₅₀) were defined as the compound
concentrations required to reduce by 50% the number of giant cells or viable cells in the
virus-infected and mock-infected cell cultures, respectively.

In the following Tables data columns are, in order:

20

HIV1 CEM: EC₅₀ in μM for inhibition of HIV-1 in CEM cells.

HIV1 CEM: EC₅₀ in μM for inhibition of HIV-2 in CEM cells.

CC50 CEM: CC₅₀ in μM for toxicity to CEM cells.

25 Table I below contains *in vitro* data comparing the biological activity of compound cf1490
with its non-phosphoramidated counterpart, Abacavir, and with the compound of
comparative Example A and its non-phosphoramidated counterpart. Abacavir is currently
used in the treatment of patients with HIV infection.

Table I

Compound	EC ₅₀ /μM	EC ₅₀ /μM	CC ₅₀ /μM	Fold Improvement
	HIV-1	HIV-2	CEM	
	CEM	CEM		
1490	0.07	0.09	13.1	30.2
Abacavir	1.9	3	78	
Example A	1.3	0.85	123	1.9
Nonphosphoramidated counterpart of Example A	2	2.3	157	

5 As can be seen in Table I compound cf 1490 embodying the present invention shows a much enhanced potency (27 to 33 fold) with respect to HIV *in vitro* than the known non-phosphoramidated Abacavir. The fold improvement in Table I is the mean increase in potency of the phosphoramidate compound versus its parent nucleoside for HIV 1 and HIV 2.

10

The surprising nature of this result is demonstrated having regard to Comparative Example A and its non-phosphoramidated counterpart. The structure of the non-phosphoramidated counterpart of Example A is *prima facie* similar to that of Abacavir. The phosphoramidate of Example A, however, shows a potency with respect to HIV which is merely comparable

15 to that of its nonphosphoramidated counterpart, whose structural formula is:

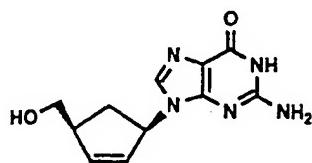


Table II below compares the *in vitro* potency data of the compound 1490 with known equivalent data disclosed in PCT/GB96/00580 for known phosphoramidated compounds. The data in each case were obtained by the *in vitro* assay described above under "*In vitro* testing"

5

Table II

Compound	EC ₅₀ /μM	EC ₅₀ /μM	CC ₅₀ /μM
	HIV-1	HIV-2	CEM
	CEM	CEM	
1490	0.07	0.09	13.1
951	0.1	0.07	5.5
1078	0.55	0.65	209
1093	0.016	0.035	2.57

Each of compounds 951, 1078 and 1093 is a phosphoramidate of a nucleoside analogue.

10 Compound 951 is 2', 3'-dideoxy -2', 3'-didehydrothymidine 5'-(phenyl exthoxyalaninyl) phosphoramidate.

Compound 1078 is 2', 3'-dideoxy -2', 3'-didehydrothymidine 5'-(phenyl dimethoxyaspartyl) phosphoramidate.

15 Compound 1093 is 2', 3'-dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphoramidate.

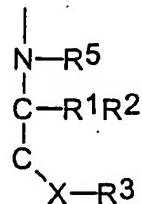
As can be seen from Table II the compound 1490 demonstrates a high degree of potency
20 with respect to HIV.

Potency and toxicity data on an expanded range of compounds is presented in Table III, in which:

Cpd and Init refer to the compound reference numbers;

X refers to the aryl (phosphate) moiety;

5 Y refers to the group;



Z refers to the bonding in the five membered sugar ring: = is unsaturated pentene;
10 H is saturated.

B in each case is "1592" which refers to the base present in Abacavir.

The data columns are, in order:

15

HIV 1 CEM: EC₅₀ in μM for inhibition of HIV1 in CEM cells

HIV2 CEM: EC₅₀ in μM for inhibition of HIV-2 in CEM cells

20

HIV2CEM.TK- EC₅₀ μM for inhibition of HIV-2 in CEM/TK⁻ cells

CC₅₀ CEM: CC₅₀ μM for toxicity to CEM cells

EC₅₀ MSV: EC₅₀ μM for inhibition of MSV

25

MCC MSV: minimum cytotoxic concentration in MSV essay.

Table III

Ord.	Unit	X	Y	Z	B	HV1 CEM	HV2 CEM	HV2 CEM,TK	OC50 CEM	EC50 MSV	MD50 MSV
1490	SH	PhO	MeAlaNH	=	1592	0.05	0.05	13.1	1.6	>4	
1540	SH	Cl	AlaNH	=	1592	1.2	0.95	11.6			
1582	SH	PhO	BzAlaNH	=	1592	0.083	0.11	-	12.6		
1683	SH	PhO	Me-D-AlaNH	=	1592	1.38	4.5	-	64.3		
1584	SH	PhO	Me(Me2Gly)NH	=	1592	0.067	0.06	-	6.91		
1585	SH	PhO	MePhen-NH	=	1592	1.42	2.13	-	36.1		
1587	SH	PhO	EtAlaNH	=	1592	0.07	0.06	-	12.1		
1588	SH	PhO	MeGlyNH	=	1592	1.78	2	-	≥100		
1589	SH	PhO	Me2AspNH	=	1592	1.42	1.9	-	44.2		
1585	SH	HO	D-AlaNH	=	1592	1.2	1.2	0.8	21.3		
1620	SH	D-CifPhO	MeAlaNH	=	1592	0.014	0.063	0.013	4.7		
1645	SH	PhO	IBuAlaNH	=	1592	3.7	6	-	33	11.7	>20
1646	SH	PhO	PrAlaNH	=	1592	0.093	0.12	-	8	2	>4
1647	SH	PhO	BuAlaNH	=	1592	0.085	0.17	-	8.23	0.62	>4
681	SH	PhO	IP(O)AlaNH	=	1592	0.5	0.85	-	9.16	2.75	>20
1671	AS	D-MeOCOC(OMe)2COPh	MeAlaNH	=	1592	0.1	0.12	-	12.1	9.2	>20
1672	AS	PhO	IP(C12)AlaNH	=	1592	0.09	0.1	-	14.4	1.98	>4
1673	AS	PhO	tBuCH2AlaNH	=	1592	0.15	0.18	-	8.07	2.92	>4
1674	AS	PhO	IP(C12)CH2AlaNH	=	1592	0.25	0.25	-	10.7	2.04	>4
1680	AHA	PhO	MeAlaNH	H	1592	12.5	17.5	-	23.7	2100	>100
1685	SS	PhO	3-pentyl-Ala NH	=	1592	1.6	2	12.6	19.7	10.1	>20
1686	SS	PhO	Meval NH	=	1592	3.5	4	3.5	54.1	11.8	>20
1687	SS	PhO	tBuCH2CH2AlaNH	=	1592	0.2	0.2	0.14	10.2	2.22	>4
1702	AHA	H	nPrAlaNH	=	1592	≥50	≥50	-	17.9	2100	>100
1708	SH	PhO	CHxAlaNH	=	1592	0.085	0.085	-	16.4	1.45	>4
1707	SH	PhO	CHxCH2AlaNH	=	1592	0.33	0.25	-	10.2	2.84	>4
1708	SH	PhO	Me(CHxCH2Gly)NH	=	1592	0.15	0.16	-	15.1	1.3	>4
1709	SH	PhO	MeProNH	=	1592	1.2	2	-	16	1.72	>4
1710	SH	4-Br-PhO	MeAlaNH	=	1592	0.0055	0.049	-	5.78	0.51	>0.8
1713	AS	4-MOCOC(Me)2COCH2	MeAlaNH	=	1592	0.053	0.065	-	1.4	10.8	>20
1714	AS	PhO	diEtAsP	=	1592	0.55	2.1	-	23.1	7.18	>20
1715	AS	PhO	MeMIET	=	1592	1.16	2.73	-	48.9	10.2	>20
1716	SS	PhO	MeAlaNH	=	1592	0.85	1.48	-	22	8.84	>20
1718	SS	PhO	MeProN	=	1592	4	5.5	-	19.4	11.8	≥100
1719	SS	PhO	Br-2-AspNH	=	1592	0.053	0.065	-	1.4		
1720	SS	PhO	IPr(CH2)3AlaNH	=	1592	0.06	0.14	-	12.6	2.2	>4
1721	SS	PhO	cPentCH2AlaNH	=	1592	0.13	0.48	-	15.2		
1722	SS	PhO	D-F-PhO	=	1592						
1737	SH	D-I-PhO	MeAlaNH	=	1592						
1738	SH	D-I-PhO	MeGlyAlaNH	=	1592						
1739	SH	PhO	Me2GlyNH	=	1592	3.5	5.33	-	36.9		
1749	AS	PhO	MeTDPNH	=	1592	9	3.67	-	18.3		
1760	AS	PhO	MeLeuNH	=	1592	7	5.53	-	24.2		
1761	AS	PhO	cHexAlaNH	=	1592	1.3	1.05	-	6.32		

Acid stability

Compounds were tested for their stability towards acid-mediated hydrolytic decomposition
 5 employing a test designed to simulate stomach conditions. Each compound was incubated in dilute HCl of pH1 for 24 hours at 25°C. 0.3mg of compound were added to 1mL of 0.1N HCl at 25°C. HPLC was run immediately for time = 0 and at intervals up to approximately 24 hours.

- 10 The results for compound 1587, and for comparative compounds labelled 1001 and 1093 and described in PCT/GB96/00580; are given in table IV below.

Table IV

Compound	Time (hr)	Compound left (%)
1587	0	100
	22	77
1001	0	0
	17	0
1093	0	100
	13	0

15

Compound 1001 disappeared immediately (<1min). Compound 1093 degraded after less than 13 hours. The majority of compound 1587 remained in tact after 22 hours.

- Each of compounds 1001 and 1093 is a phosphoramidate of an adenosine analogue.
 20 Compound 1001 is 2',3' -dideoxy -2',3' didehydroadenosine-5'- (phenylimethoxyalaninyl) phosphate. Compound 1093 is 2'3' -dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphate.

- The results given in Table V above demonstrate the acid stability of a compound
 25 embodying the present invention compared to known compounds.

Biological stability

Compound 1587 of the present invention and the two comparative compounds 1001 and 1093 identified above were tested for their stability towards biological decomposition.

- 5 Each compound was incubated in normal heparinised human plasma at 37°C for 4 hours. At selected time points (0, 15, 30 min, and 1, 2, 4 hours) duplicate samples were removed and deproteinated by acetonitrile extraction. Drug concentrations were then determined by LC/MS/MS analysis using standard methods. The results are shown in Table V below.

10

Table V

Compound	% Remaining at 4 hours	Half-life (hours)
1587	91	26
1001	52	4.6
1093	50	4.2

Under the conditions of the test the data in Table V shows a 6-fold stability advantage of compound 1587 over each of compounds 1001 and 1093.

15

20

25

Example 1**(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl ethoxy-L-alaninyl) phosphate Succinate Salt**

5

(a) Phenylethoxy-L-alaninyl phosphorochloridate

L-alanine ethyl ester hydrochloride (3.0 g, 0.02 moles) was suspended in dry methylene chloride (40 mL). To this suspension was added phenyl phosphorodichloridate (2.9 mL, 0.02 mol) and the mixture was cooled to -80 °C. N,N-Diisopropylethylamine (Aldrich, 6.8 mL, 0.04 mol) was added to the reaction in aliquots (1-2 mL) over a 1 h time period. Reaction allowed to warm slowly to room temperature while stirring for 2 h. Organic solvent was removed in vacuo and the residue treated with diethyl ether (100 mL). The diethyl ether solution was filtered to remove insoluble inorganics and concentrated in vacuo to give the product as a colourless syrup. This product was used without further 15 purification in part b.

**(b) (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl ethoxy-L-alaninyl)phosphate**

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol (1.5 20 g, 5.2 mmol) was dried by addition of dioxane and concentration in vacuo. To the dried nucleoside was added anhydrous pyridine (10 mL) and tetrahydrofuran (20 mL). Subsequently, tert-butyl magnesium chloride (6 mL, 1M solution in tetrahydrofuran, 6 mmol) was added slowly. The reaction was stirred for 20 min and a solution of phenyl ethoxy-L-alaninyl phosphorochloridate (part a, 3 g, 0.01 mol in 20 mL tetrahydrofuran) 25 was added. The reaction was stirred at room temperature for 10 h and subsequently concentrated in vacuo to a brown syrup. This syrup was dissolved in methylene chloride (100 mL) the methylene chloride extracted with water (2x100 mL), dried ($MgSO_4$), filtered and concentrated to a brown solid foam. This solid foam was purified by flash chromatography using 5% methanol in chloroform as eluent to give 1.7 g (60 %) of, after 30 purification, a 4:6 mixture of the phosphate isomers as a white solid foam. 1H -NMR ($CDCl_3$): δ 7.47 (2 x s, 1H), 7.10-7.46 (m, 5H), 6.07 (m, 1H), 5.9 (m, 1H), 5.78 (s, 1H), 5.5 (m, 1H), 4.84 (bs, 2H), 4.1 (m, 4H), 4.00 (m, 1H), 3.64 (m, 1H), 3.14 (m, 1H), 3.0 (m, 1H),

108

2.78 (m, 1H), 1.68 (m, 1H), 1.36 (2xd, 3H), 1.22 (2xt, 3H), 0.86 (m, 2H), 0.6 (m, 2H); ^{31}P -NMR (CDCl_3): δ 3.05, 3.02.

Anal. Calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_7\text{O}_5\text{P} \times 1/4 \text{CHCl}_3$: C, 53.07; H, 5.70; N, 17.15. Found: C, 52.81; H, 5.95; N, 16.91.

5

(c) (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Succinate Salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (part 1b, 376 mg, 0.7 mmol) was dissolved in ethanol. To this solution was added succinic acid (82 mg, 0.7 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10-20 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 330 mg (72 %) of a 4:6 mixture of the phosphate isomers as a solid; $^1\text{H-NMR}$ (DMSO-d_6): δ 12.14 (s, 2H), 7.58 (s, 1H), 7.1-7.4 (m, 6H), 5.9-6.1 (m, 3H), 5.85 (broad s, 2H), 5.42 (m, 1H), 3.95-4.15 (m, 4H), 3.8 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 2.4 (s, 4H), 1.63 (m, 1H), 1.4 (2xd, 3H), 1.12 (t, 3H), 0.5-0.7 (m, 4H); $^{31}\text{P-NMR}$ (DMSO-d_6): δ ; 4.00 and 3.68; high resolution mass spectrum: calcd for $\text{C}_{25}\text{H}_{32}\text{N}_7\text{O}_5\text{P} (\text{M}+\text{H})^+$ (m/z) 542.2281, found 542.2282.

Anal. Calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_7\text{O}_5\text{P} \cdot \text{C}_4\text{H}_6\text{O}_4 \cdot 1/2\text{H}_2\text{O}$: C, 52.09; H, 5.87; N, 14.66. Found: C, 52.13; H, 5.72; N, 14.61.

Example 2

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Succinate Salt

(a) Phenylmethoxy-L-alaninyl phosphorochloridate.

L-alanine methyl ester hydrochloride (10 g, 0.072 mol) was suspended in dry methylene chloride (100 mL). To this suspension was added phenyl phosphorodichloridate (10.7 g, 7.6 mL) and the mixture was cooled to -80 °C. Subsequently N,N-Diisopropylethylamine (Aldrich, 25 mL) was added to the reaction in aliquots (1-2 mL) over a 1 h time period. The solution was stirred for 30 min at -80°C, then allowed to warm slowly to room temperature while stirring for 2 h. Organic solvent was removed in vacuo and the residue

treated with diethyl ether (100 mL). The diethyl ether solution was filtered to remove insoluble inorganics and concentrated in vacuo to give the product as a colorless syrup: ^{31}P -NMR (CDCl_3) δ 8.61; 8.37 ppm. This product was used without further purification in Example 2b

5

(b) (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol (5.5 g, 0.018 moles) was dried by addition of dioxane and concentration in vacuo. To the dried 10 nucleoside was added anhydrous tetrahydrofuran (30 mL) and pyridine (40 mL). Subsequently tert-butyl magnesium chloride (23 mL, 1M solution in tetrahydrofuran, 1.3 equivalents) was added slowly. The reaction was stirred for 20 min and a solution of phenylmethoxy-L-alaninyl phosphorochloridate (12 g, 0.043 moles, 2.5 equivalents in 20 mL THF) was added. The reaction was stirred at room temperature for 12 h and 15 subsequently concentrated in vacuo to a brown syrup. This syrup was dissolved in methylene chloride (100 mL) the methylene chloride extracted with water (2x100 mL), dried (MgSO_4), filtered and concentrated to a brown foam. This foam was purified by flash chromatography using 5% methanol in chloroform as eluent to give 6.9 g (75 %) of a mixture of the phosphate isomers of the title compound as a white solid foam. ^1H -NMR 20 (CDCl_3): δ 7.5 (2 x s, 1H), 7.1-7.4 (m, 5H), 6.1 (m, 1H), 5.9 (m, 2H), 5.5-5.6 (m, 1H), 4.9 (bs, 2H), 4.2 (m, 2H), 4.05 (m, 1H), 3.7 (s, 3H), 3.6-3.8 (m, 1H) 3.17 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.7 (m, 1H), 1.4 (2 x d, 3H), 0.9 (m, 2H), 0.6 (m, 2H); ^{31}P -NMR (CDCl_3): δ 3.07, 3.02.

Anal. Calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_7\text{O}_5\text{P} \times 2/5 \text{CHCl}_3$: C, 50.94; H, 5.33; N, 17.00. Found: C, 25 50.83; H, 5.39; N, 16.94.

(c) (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Succinate Salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O- 30 (phenyl methoxy-L-alaninyl)phosphate (part b, 100 mg, 0.19 mmol) was dissolved in methanol. To this solution was added succinic acid (22 mg, 0.19 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator

overnight and solid collected by filtration to give 70 mg (57%) of a mixture of the phosphate isomers as a solid; $^1\text{H-NMR}$ (DMSO-d₆): δ 12.15 (s, 2H, D₂O exchangeable), 7.61 (s, 1H), 7.36 (3H, becomes 2H on D₂O exchange), 7.20 (3H), 5.9-6.1 (m, 3H), 5.88 (broad s, 2H, D₂O exchangeable), 5.44 (m, 1H), 4.0-4.2 (m, 2H), 3.85 (m, 1H), 3.60 (s, 5 3H), 3.05 (2H), 2.65 (m, 1H), 2.44 (s, 4H), 1.64 (m, 1H), 1.23 (m, 3H), 0.5-0.7 (m, 4H); $^{31}\text{P-NMR}$ (DMSO-d₆): δ ; 3.99 and 3.66;
Anal. Calcd. for C₂₄H₃₀N₇O₅P · C₄H₆O₄·1/2H₂O: C, 51.38; H, 5.70; N, 14.98. Found: C, 51.36; H, 5.66; N, 14.99.

10 Example 3

**(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl ethoxy-L-alaninyl) phosphate Fumarate Salt**

15 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (198 mg, 0.37 mmol) was dissolved in ethanol. To this solution was added fumaric acid (43 mg, 0.37 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and 20 solid collected by filtration to give 185 mg (75 %) of a 4:6 mixture of the phosphate isomers as a solid; $^1\text{H-NMR}$ (DMSO-d₆): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 6.64 (s, 2H), 5.9-6.1 (m, 3H), 5.87 (broad s, 2H), 5.44 (m, 1H), 3.95-4.15 (m, 4H), 3.84 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 1.63 (m, 1H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); $^{31}\text{P-NMR}$ (DMSO-d₆): δ ; 4.00 and 3.67.
25 Anal. Calcd. for C₂₅H₃₂N₇O₅P · C₄H₄O₄·1/2H₂O: C, 52.25; H, 5.59; N, 14.71. Found: C, 52.25; H, 5.51; N, 14.49.

Example 4

**30 (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl ethoxy-L-alaninyl) phosphate Glutarate Salt**

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (part 1b, 200 mg, 0.38 mmol) was dissolved in ethanol. To this solution was added glutaric acid (50 mg, 0.38 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with 5 heating. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 130 mg (50 %) of a 67:33 mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 5.9-6.1 (m, 3H), 5.87 (broad s, 2H), 5.44 (m, 1H), 3.95-4.2 (m, 4H), 3.8 (m, 1H), 3.1 (m, 2H), 2.65 (m, 1H), 2.25 (t, 4H), 1.7 (m, 3H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ; 4.00 and 3.68.

10 Anal. Calcd. for C₂₅H₃₂N₇O₅P·C₅H₈O₄·1/2H₂O: C, 52.78; H, 6.05; N, 14.36. Found: C, 52.97; H, 6.07; N, 14.33.

Example 5

15 (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate D-Tartrate Salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (157 mg, 0.29 mmol) was dissolved in ethanol. To 20 this solution was added D-tartaric acid (44 mg, 0.29 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 112 mg of a 53:47 mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 5.8-6.2 (m, 5H), 5.44 (m, 1H), 4.3 (s, 2H), 3.95-4.2 (m, 4H), 3.8 (m, 1H), 3.35 (broad s, 2H), 3.1 (m, 2H), 2.65 (m, 1H), 1.7 (m, 1H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ; 4.00 and 3.67.

Example 6

30 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Diastereomers

An approximately 1:1 mixture of diastereomers of (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate was prepared using similar methodology as above: $^1\text{H-NMR}$ (CDCl_3): δ 7.5 (2 x s, 1H), 7.1-7.4 (m, 5H), 6.1 (m, 1H), 5.9 (m, 2H), 5.5-5.6 (m, 1H), 4.9 (bs, 2H), 5 4.2 (m, 2H), 4.05 (m, 1H), 3.7 (s, 3H), 3.6-3.8 (m, 1H) 3.17 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.7 (m, 1H), 1.4 (2 x d, 3H), 0.9 (m, 2H), 0.6 (m, 2H); $^{31}\text{P-NMR}$ (CDCl_3): δ 3.07, 3.02.

Anal. Calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_7\text{O}_5\text{P} \times 2/5 \text{CHCl}_3$: C, 50.94; H, 5.33; N, 17.00. Found: C, 50.83; H, 5.39; N, 16.94.

10 The phosphate isomers were separated with Supercritical Fluid Chromatography using a Chiralpak AS column, 25 % methanol in carbon dioxide as the eluent, flow rate 2 mL/min, temperature 40°C, and pressure 3000psi. The first isomer to elute had a RT of 2.9 min and was 100% enantiopure; evaporation of solvents gave the isomer as a white solid foam: $^1\text{H-NMR}$ (CDCl_3): δ 7.50 (s, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 6.11 (m, 1H), 5.91 (m, 1H), 5.86 (s, 1H), 5.55 (m, 1H), 4.89 (s, 2H), 4.24 (m, 2H), 4.05 (m, 1H), 3.72 (s, 3H), 15 3.65 (m, 1H), 3.20 (m, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 1.72 (m, 1H), 1.37 (d, 3H), 0.89 (m, 2H), 0.62 (m, 2H); $^{31}\text{P-NMR}$ (CDCl_3): δ 3.07.

Anal. Calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_7\text{O}_5\text{P} \times 1/7 \text{CHCl}_3$: C, 53.25; H, 5.58; N, 18.00. Found: C, 20 53.27; H, 5.69; N, 17.72.

The second isomer to elute had a RT of 6.7 min and was 100% enantiopure; evaporation of solvents gave the isomer as a white solid foam: $^1\text{H-NMR}$ (CDCl_3): δ 7.52 (s, 1H), 7.25-7.4 (m, 2H), 7.15-7.22 (m, 3H), 6.11 (m, 1H), 5.94 (m, 1H), 5.85 (s, 1H), 5.55 (m, 1H), 4.88 (m, 2H), 4.22 (m, 2H), 4.04 (m, 1H), 3.75 (s, 3H), 3.7-3.75 (m, 1H), 3.17 (m, 1H), 3.04 (m, 1H), 25 2.80 (m, 1H), 1.73 (m, 1H), 1.42 (d, 3H), 0.89 (m, 2H), 0.67 (m, 2H); $^{31}\text{P-NMR}$ (CDCl_3): δ 3.0.

Anal. Calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_7\text{O}_5\text{P} \times 1/5 \text{CHCl}_3$: C, 52.71; H, 5.52; N, 17.78. Found: C, 52.61; H, 5.67; N, 17.53.

**(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl N-methylamino-L-alaninyl) phosphate Sodium Salt**

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (0.060 g, 0.11 mmoles) was suspended in solution of 40% aqueous methylamine (60 ml) and stirred at room temperature for 18 hours. The volatiles were removed by spin evaporation *in vacuo* and the residue was dissolved in water (50 ml), extracted with dichloromethane (2x50 ml) and purified by anion exchange chromatography on a Sep-Pak® Vac 35cc Accell™ Plus QMA cartridge (Waters Corp., P/N WAT054725) (HCO₃⁻ form) with an aqueous ammonium bicarbonate buffer (0 - 0.5 M gradient, 1 L). The appropriate fractions were combined and the volatiles were remove by spin evaporation *in vacuo*. The residue was twice dissolved in deionized water and spin evaporated *in vacuo* to give (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate as the ammonium salt. This salt was dissolved in deionized water and passed through a Sep-Pak® Vac 20cc Accell™ Plus CM cartridge (Waters Corp., P/N WAT054675) (Na⁺ form) using deionized water. The appropriate fractions were combined and lyophilized to give 0.026 g (46% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt 2.2 hydrate as a white solid. MS (ES) *m/e* 449 (MH⁺).

Anal. Calcd. for C₁₈H₂₆N₈NaO₄P · 2.2 H₂O: C, 42.22; H, 5.98; N, 21.88. Found: C, 42.36; H, 5.77; N, 21.66.

Example 8

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate Sodium Salt

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt was prepared by a method analogous to that used to prepare (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt except that the 40% aqueous methylamine solution was replaced by

a solution of cyclopropylamine (5 ml, 72 mmoles) in deionized water (50 ml).

Lyophilization of the combined fractions gave 35 mg (58% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt 2.5 hydrate as a white solid: MS

5 (ES⁻) *m/e* 475 (MH⁺).

Anal. Calcd. for C₂₀H₂₈N₈NaO₄P · 2.5 H₂O: C, 44.20; H, 6.12; N, 20.61. Found: C, 44.27; H, 5.81; N, 20.49.

Example 9

10

**(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate Sodium Salt**

15 (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-dimethylamino-L-alaninyl) phosphate sodium salt was prepared by a method analogous to that used to prepare (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt except that the 40% aqueous methylamine solution was replaced by a 40% aqueous dimethylamine solution (50 ml). Lyophilization of the combined fractions gave 20 39 mg (59% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate sodium salt trihydrate as a white solid: MS (ES⁻) *m/e* 463 (MH⁺).

Anal. Calcd. for C₁₉H₂₈N₈NaO₄P · 3.0 H₂O: C, 42.22; H, 6.34; N, 20.73. Found: C, 42.40; H, 6.01; N, 20.51

25

Example 10

**(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol
O-(L-alaninyl) phosphate Disodium Salt**

30

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (0.5 g, 0.95 mmoles) was suspended in solution of triethylamine (30 ml) and deionized water (30 ml) and stirred at room

temperature for 18 hours. The volatiles were removed by spin evaporation *in vacuo* and the residue was dissolved in water (50 ml), extracted with dichloromethane (2x50 ml) and purified by anion exchange chromatography on a Sep-Pak® Vac 35cc Accell™ Plus QMA cartridge (Waters Corp., P/N WAT054725) (HCO_3^- form) with an aqueous ammonium bicarbonate buffer (0 - 0.5 M gradient, 1 L). The appropriate fractions were combined and the volatiles were remove by spin evaporation *in vacuo*. The residue was twice dissolved in deionized water and spin evaporated *in vacuo* to give (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate as the ammonium salt. This salt was dissolved in deionized water and passed through a Sep-Pak® Vac 20cc Accell™ Plus CM cartridge (Waters Corp., P/N WAT054675) (Na^+ form) using deionized water. The appropriate fractions were combined and lyophilized to give 0.430 g (86% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate disodium salt 2.5 hydrate as a white solid: MS (ES) *m/e* 436 (MH^+).
Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_7\text{Na}_2\text{O}_5\text{P} \cdot 2.5 \text{ H}_2\text{O}$: C, 38.79; H, 5.17; N, 18.63. Found: C, 38.62; H, 5.11; N, 18.43.

20

25

30

Anti-Hepatitis B Virus Activity

Compounds of Example 1 to 10 were tested for anti- Hepatitis B Virus activity according to the method described by Jansen, R. et al., *Antimicrobial Agents and Chemotherapy*, 5 Vol. 37, No. 3, pp. 441-447, 1993. Representative IC₅₀ values were in the range of 0.017μM – 3.0 μM.

The solubility and solution/solid state stability of three salt forms of (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol O- (phenyl 10 ethoxy-L-alaninyl) phosphate

The salts have handling and formulation advantages in that they are stable, free-flowing crystalline solids that do not change composition, even at elevated temperature and humidity. The free base of (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-15 2-cyclopentene-1-methanol O- (phenyl ethoxy-L-alaninyl) phosphate in contrast, is a hygroscopic, amorphous solid foam that could not be crystallized.

Form	Solid Type*	0.1 N HCl		PBS		HPMC/Tween		Solid State Stability (%)
		Solubility (mg/mL)	Stability (%)	Solubility (mg/mL)	Stability (%)	Solubility (mg/mL)	Stability (%)	
Free Base	Amorphous Hygroscopic	> 5	69.1	0.054	98.5	0.04	97.6	93.7
Glutarate	crystals	> 5	69.3	0.084	99.9	> 0.25, < 1	98.6	98.9
Fumarate	crystals	> 5	70.0	0.086	98.5	0.22	98.3	97.1
Succinate	crystals	> 5	66.0	0.069	99.8	> 0.25, < 1	98.8	99.6

Solution stability = % of parent (AUC) after 27 hr at room temperature, normalized to initial AUC.

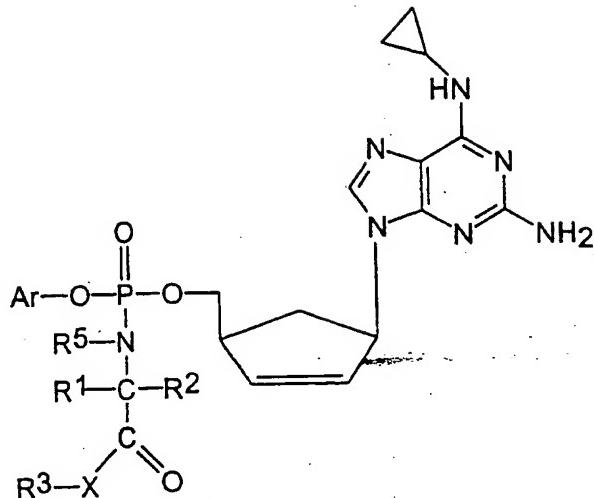
20 Solid state stability = % of parent (AUC) after two weeks at 60°C, normalized to initial AUC.

The free bases of the phosphoramidates of 2',3'-dideoxy adenosine and 2',3'-dideoxy-2',3'-didehydroadenosine are hygroscopic amorphous foams or gums. However, their 25 instability to acid prevents advantageous utilization of complexes with acids to form salts

with improved physical properties; exposure to acids degrades these compounds rapidly. (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol (abacavir) has enhanced stability to acid, compared to nucleosides containing labile glycosidic bonds between heterocycle and sugar. Thus phosphoramidate protides of 5 abacavir form stable salts that have been found to have advantageous physical properties suitable for pharmaceutical development.

CLAIMS

1. A compound of the formula (I):



5

wherein

Ar is an aryl group

10 R^1 and R^2 are each independently selected from the group comprising H, alkyl and aryl groups;

X is selected from the group comprising O, NH, NR⁴ and S wherein R⁴ is selected from the group comprising alkyl and aryl;

15 R⁵ is selected from the group comprising H, alkyl and aryl groups, wherein when R^1 and R^5 are each alkyl they may be linked to form a 5- or 6-membered ring;

20 and R^3 is selected from the group comprising H, alkyl, aryl, heterocyclic and polycyclic groups,

or a pharmaceutically acceptable derivative or metabolite thereof.

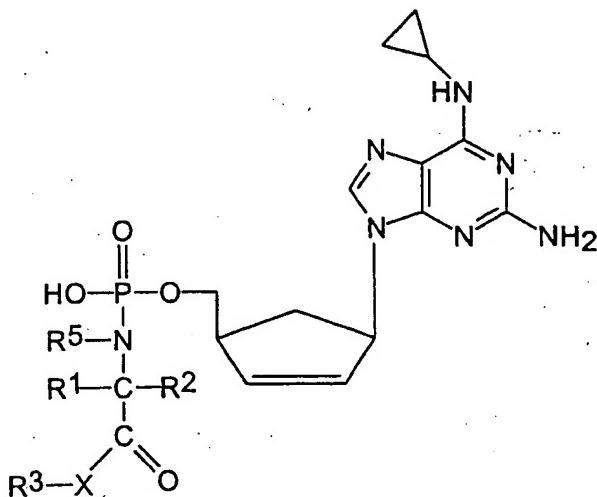
2. A compound according to claim 1 wherein

Ar is phenyl or substituted phenyl.

5 3. A compound according to any one of claims 1 to 2 wherein R³ is selected from the group comprising -CH₃, -C₂H₅ and -CH₂Ph.

4. A compound of the formula (II):

10



wherein R¹, R², R³, R⁵ and X have the meanings ascribed in Claim 1.

5. A compound according to any one of claims 1 to 4 wherein R¹ and R² are the same
15 or different and are H, -CH₃ or -CH₂CH₃.

6. A compound according to any one of claims 1 to 4 wherein R¹ is H and R² is -CH₃
or -CH₂-Ph.

20 7. A compound according to any one of claims 1 to 6 wherein the C atom bearing R¹
and R² is chiral.

120

8. A compound according to any one of claims 1 to 6 wherein the compound has L chirality with respect to the C atom bearing R¹ and R².

9. A compound according to any one of claims 1 to 8 wherein X is O.

5

10. A compound selected from:

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-alaninyl] phosphate

10

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[L-alaninyl] phosphate diammonium salt

15

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl benzyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-D-alaninyl] phosphate

20

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α,α -dimethylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-phenylalaninyl] phosphate

25

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl ethoxy-L-alaninyl] phosphate

30

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxyglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl L-aspartyl dimethyl ester] phosphate.

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-chlorophenyl methoxy-L-alaninyl] phosphate

5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl tertbutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-propoxy-L-alaninyl] phosphate

10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-butyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-15 [Phenyl i-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[(p-(2",2"-dimethoxypropionic acid methyl ester) phenyl) methoxy-L-alaninyl] phosphate

20 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl (2-methylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl (2,2-dimethylpropyl)oxy-L-alaninyl] phosphate

25 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-methylbutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-30 [phenyl 3-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-valinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3,3-dimethyl-1-butyloxy-L-alaninyl] phosphate

5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl cyclohexyloxy-L-alaninyl] phosphate

10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl cyclohexanemethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-
15 [Phenyl methoxy-3-cyclohexane-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-bromophenyl methoxy-L-alaninyl] phosphate

20 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl diethoxy-L-aspartyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-methionyl] phosphate

25 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-leucinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-
30 [phenyl methoxy-L-prolinyl] phosphate.

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methylene-
[phenyl dibenzylloxy-L-aspartinyl] phosphate

- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-methyl-1-pentyloxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopentylmethoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-fluorophenyl methoxy-L-alaninyl] phosphate
- 10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-iodophenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl dimethoxy-L-glutamyl] phosphate
- 15 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-tryptophanyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-isoleucinyl] phosphate
- 20 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cycloheptyloxy-L-alaninyl] phosphate
- 25 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclobutylmethoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopropylmethoxy-L-alaninyl] phosphate
- 30 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclobutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopentyloxy-L-alaninyl] phosphate

5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl phenethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-phenyl-1-propoxy-L-alaninyl] phosphate

10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-phenyl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 2-cyclohexyl-1-ethoxy-L-alaninyl] phosphate

15 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-cyclohexyl-1-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-cyclohexyl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -ethyl-L-glycanyl] phosphate

25 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -phenyl(RS)glycanyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -propyl-L-glycanyl] phosphate)

30 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -butyl-L-glycanyl] phosphate

- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-phenoxyphenyl methoxy-L-alaninyl]phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-phenylphenyl methoxy-L-alaninyl]phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-hydroxyacetophenone methoxy-L-alaninyl] phosphate
- 10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-butylphenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-methoxyphenyl methoxy-L-alaninyl] phosphate
- 15 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-propoxypyhenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-
- 20 [phenyl methoxy- α,α -cyclopentylglycinyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α,α -cylohexylglycinyl] phosphate
- 25 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α,α -cyclopropylglycinyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(methoxycarbonyl)phenyl methoxy-L-alaninyl] phosphate
- 30 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(trifluoromethylthio)phenyl methoxy-L-alaninyl] phosphate

- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2-methoxyvinyl)phenyl methoxy-L-alaninyl] phosphate
- 5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2-phenylcarbonylvinyl)phenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2,2-dicyanovinyl)phenyl methoxy-L-alaninyl] phosphate
- 10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[o-(carboxylate ethyl ester)phenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate succinate salt
- 15 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl) phosphate succinate salt
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate fumarate salt
- 20 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate glutarate salt
- 25 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate D-tartrate salt
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl) phosphate diastereoisomers
- 30 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-
5 (phenyl N,N-dimethylamino-L-alaninyl) phosphate sodium salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate disodium salt.

10 11. A compound according to any one of claims 1 to 10 for use in a method of treatment, prophylaxis or diagnosis.

12. Use of a compound according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment or prophylaxis of a viral infection.

15

13. Use of a compound according to claim 12 wherein the viral infection comprises HIV.

14. Use of a compound according to claim 12 wherein the viral infection comprises
20 HBV.

15. A method of prophylaxis or treatment of viral infection comprising administration to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 10.

25

16. A method according to claim 15 wherein the viral infection is HIV.

17. A method according to claim 15 wherein the viral infection is HBV.

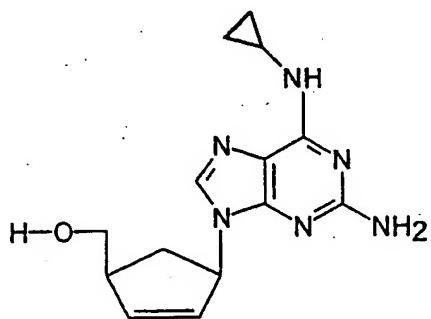
30 18. A method according to any one of claims 15 to 17 comprising administering orally to a patient an effective dose of the compound.

19. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 in combination with a pharmaceutically acceptable excipient.

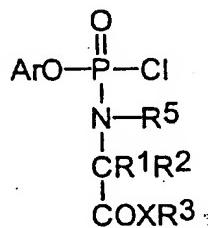
20. A composition according to claim 19 in a form for oral administration.

5

21. A process for the preparation of a compound according to any one of claims 1 to 10 comprising reacting a compound having the formula



10 with a compound of formula



INTERNATIONAL SEARCH REPORT

National Application No PCT/GB 99/03207
--

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07F9/6561 A61K31/675
--

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
--

C. DOCUMENTS CONSIDERED TO BE RELEVANT
--

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 434 450 A (THE WELLCOME FOUNDATION LTD.) 26 June 1991 (1991-06-26) the whole document	1-21
Y	WO 96 29336 A (MEDICAL RESEARCH COUNCIL) 26 September 1996 (1996-09-26) cited in the application the whole document	1-21
Y	EP 0 369 409 A (BRISTOL-MYERS SQUIBB CO.) 23 May 1990 (1990-05-23) the whole document	1-21
Y	EP 0 468 866 A (MERRELL DOW PHARMACEUTICALS INC.) 29 January 1992 (1992-01-29) the whole document	1-21
		-/-

<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.
--

<input checked="" type="checkbox"/> Patent family members are listed in annex.
--

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed Invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed Invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
21 December 1999	11/01/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Beslier, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03207

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 06102 A (MEDIVIR AB) 16 April 1992 (1992-04-16) the whole document	1-21

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/03207

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 15-18 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No	
PCT/GB 99/03207	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 434450 A	26-06-1991	AP 196 A AT 181917 T AU 633672 B AU 6841990 A CA 2033044 A CN 1054981 A,B CZ 9202470 A CZ 9006583 A DE 69033197 D DE 69033197 T EP 0921121 A EP 0921114 A ES 2133138 T FI 906367 A FI 970666 A IL 96748 A JP 11158160 A MX 9203215 A NZ 236593 A PL 167097 B PT 96321 A,B SG 49685 A RU 2068849 C RU 2091386 C US 5206435 A	30-06-1992 15-07-1999 04-02-1993 27-06-1991 23-06-1991 02-10-1991 15-04-1998 12-11-1997 12-08-1999 28-10-1999 09-06-1999 09-06-1999 01-09-1999 23-06-1991 17-02-1997 31-07-1995 15-06-1999 01-07-1992 26-01-1994 31-07-1995 30-09-1991 15-06-1998 10-11-1996 27-09-1997 27-04-1993
WO 9629336 A	26-09-1996	AU 707196 B AU 5009496 A CA 2215190 A EP 0820461 A JP 11506419 T NZ 303711 A	08-07-1999 08-10-1996 26-09-1996 28-01-1998 08-06-1999 25-02-1999
EP 369409 A	23-05-1990	AT 116654 T CA 2001715 A DE 68920413 D DE 68920413 T ES 2066828 T JP 2178295 A JP 2743099 B US 5744600 A	15-01-1995 14-05-1990 16-02-1995 11-05-1995 16-03-1995 11-07-1990 22-04-1998 28-04-1998
EP 468866 A	29-01-1992	EP 0468119 A AU 8110991 A CA 2047390 A CN 1059528 A FI 913533 A JP 4330086 A NO 912874 A PT 98425 A	29-01-1992 30-01-1992 25-01-1992 18-03-1992 25-01-1992 18-11-1992 27-01-1992 29-05-1992
WO 9206102 A	16-04-1992	AU 8641091 A CA 2093020 A EP 0554274 A JP 6501261 T PT 99130 A US 5473063 A US 5952500 A	28-04-1992 03-04-1992 11-08-1993 10-02-1994 31-08-1992 05-12-1995 14-09-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/GB 99/03207

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9206102 A		US 5747473 A	05-05-1998

THIS PAGE BLANK (USPTO)